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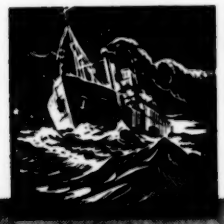

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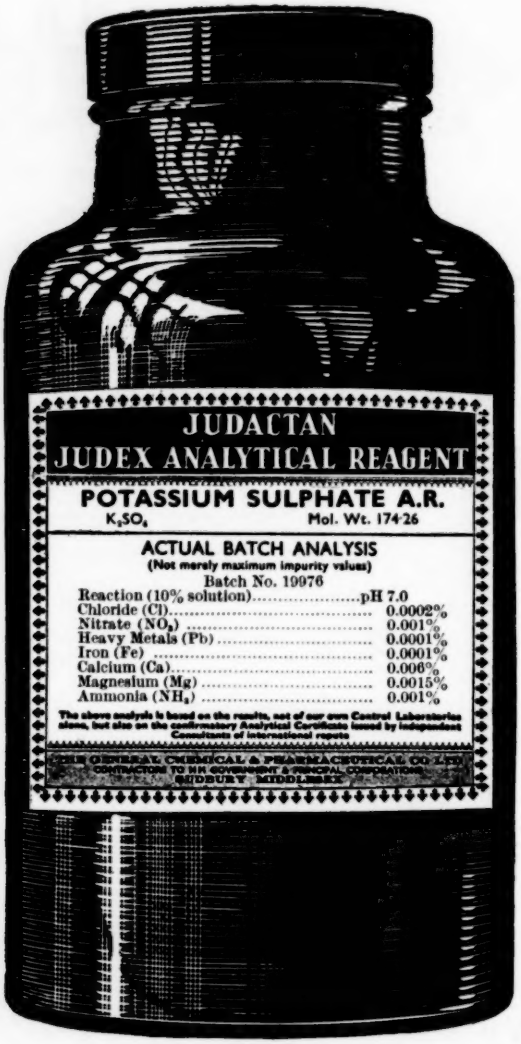

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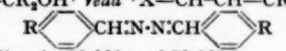
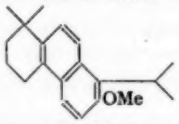
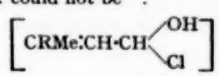
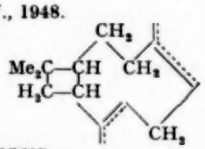
ERRATA.

Vol.	Page.	Line.	
1950	456		Table III, compound (46) for 4-*Chloro*-2-*methylthio*-6-*methyl*- read 4-*Chloro*-2-*methylthio*-5-*methyl*-.
	1402	3 *	*for* as above *read* unity.
	1403	2	for $E_1 = AB$; $E_2 = DE$ read $xE_1 = AB$; $xE_2 = DE$.
1951	1515	8 *	*for* 4-formyl-3 : 5-dimethylphenol *read* 2-formyl-3 : 5-dimethylphenol.
	1599	8 *	for 2-*Di*-p-*dimethylaminophenyl*-2-*methylpropan*-1-*one* read 1 : 2-*Di*-p-*dimethylaminophenyl*-2-*methylpropan*-1-*one*.
	2089	9 *	*for* $X^-{=}CH{-}CH{=}CR_2OH^+$ *read* $^+X{=}CH{-}CH{=}CR_2{\cdot}OH^-$.
	2203		Formula (VI) *should read* 
	2340		Table I, first column, third line *for* 70·00° *read* 70·80°.
	2570	21 *	*for* $[\alpha]_D^{25}$ +70·5° *read* $[\alpha]_D^{25}$ −26·1°.
	2844		Fig. 1, the caption at the top of the figure should read [NOCl *concn.*]^2 *Curve B*.
	2960		Eqn. 10 *should read* $x_B^s = n_B^s/(n_A^s + n_B^s)$ $= \dfrac{A(x_B + \Delta x_B) - a_A(n_A + n_B)\Delta x_B}{A + (n_A + n_B)(a_B - a_A)\Delta x_B}$
	2979		Formula (II) *should read* 
	3060	13 *	*for* Na[Ln enta],H_4enta *read* 4Na[Ln enta],H_4enta.
	3089	3 *	*for* reaction *read* relation.
	3091	12	*for* $(\partial P/\partial T)_T$ read $(\partial P/\partial T)_V$.
	3092	28	*for* syphon *read* sylphon.
	3163	5	*after* R·CH(OH)·CHR′·COR″ *insert* + B.
	3166	4 and 5	*should read* Glycine ethyl ester hydrochloride was condensed with acetylacetone in buffer solution. On account of the appreciable solubility of the product in water, excess of the buffer could not be .
	3256		The formula between (VII) and (VI) *should read* 
	3345	21 *	for *J.*, 1947, read *J.*, 1948.
	3384		Formula (VI) *should read* 
	3420		*for* Franzel *read* Franzen.
1952	219		The numbers (X) and (XI) should be below the second and the fourth formula, respectively. The double arrow between the third and the fourth formula should be replaced by a double-headed arrow ⟷.
	275	23 *	*for* 15 000 *read* 13 000.
		12 *	*for* 14 000 *read* 13 000.
		last	*for* 10 000 *read* 9000.
		,,	*for* 12 500 *read* 11 500.
	276	3	*for* 7000 *read* 6500.
	727	29 *	*for* α-amylase *read* β-amylase.

* From bottom of page.

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136. *On the Chemical Kinetics of Autosynthetic Systems.*

By Sir Cyril N. Hinshelwood.

A general treatment is given of the chemical kinetics of certain types of co-ordinated reactions. It is shown that where several components are synthesised by the use of mutually supplied intermediates there is a steady state in which each separate component increases according to the simple exponential law of autosynthesis. Before the steady state is reached there may be lag phases, or even periodic variations in rate. The conditions under which the kinetic equations can be applied to material subject to cell division are considered. Changes of proportions accompanying transfer to new media or to media containing inhibitors are shown to be possible, and the rate and relative permanence of these adaptive changes are discussed.

The relation of the equations derived to the phenomena shown by living cells is indicated, and a hypothesis about the mode in which new enzymes may arise in response to new substrates is outlined.

Masses of living matter reduplicate themselves by processes involving an elaborate co-ordination of enzyme reactions. Quite apart from their biological significance such systems present problems which are novel and important from the point of view of chemical kinetics generally. Various kinetic propositions about autosynthetic mechanisms have been formulated from time to time in connexion with experimental studies of bacterial growth made in this laboratory, but they have been published in various places and sometimes in biological journals. The object of this paper is partly to collect and systematise some of these propositions, partly to elaborate and extend them, and partly to indicate the chemical interest of the biological facts without any obscuring of the issues by bacteriological technicalities.

Equations of Autosynthesis.—In constant surroundings living matter such as that contained in a unicellular organism reproduces all its parts according to the equation

$$dX/dt = kX \text{ or } X = X_0e^{kt} \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad (1)$$

This occurs by the interplay of enzyme reactions. Yet enzymes in isolation do not increase autocatalytically, so the origin of equation (1) is of interest.

Suppose we have two enzymes each of which increases its substance by the addition of something derived from the working of the other. Then we shall have

$$dX/dt = \alpha Y \text{ and } dY/dt = \beta X \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad (2)$$

The solutions of these equations are

$$X = P_1e^{kt} + Q_1e^{-kt} \text{ and } Y = P_2e^{kt} + Q_2e^{-kt} \quad . \quad . \quad . \quad . \quad (3)$$

where $P_1 + Q_1 = X_0$ and $P_2 + Q_2 = Y_0$, X_0 and Y_0 being the amounts of X and Y at time zero.

It follows that

$$X = \tfrac{1}{2}\left(X_0 + \frac{\alpha}{k}Y_0\right)e^{kt} + \tfrac{1}{2}\left(X_0 - \frac{\alpha}{k}Y_0\right)e^{-kt} \quad . \quad . \quad . \quad . \quad (4a)$$

$$Y = \tfrac{1}{2}\left(Y_0 + \frac{k}{\alpha}X_0\right)e^{kt} + \tfrac{1}{2}\left(Y_0 - \frac{k}{\alpha}X_0\right)e^{-kt} \quad . \quad . \quad . \quad . \quad (4b)$$

where $\alpha\beta = k^2$.

When t is sufficiently great the terms in e^{-kt} vanish and the ratio X/Y assumes the constant value $\left(X_0 + \frac{\alpha}{k}Y_0\right)\Big/\left(Y_0 + \frac{k}{\alpha}X_0\right) = \alpha/k$. If now a portion of the system in which this constant ratio is established is separated and becomes the starting point of

a new autosynthetic system (as when bacteria are subcultured), $X_0/Y_0 = \alpha/k$. In these circumstances (4*a*) and (4*b*) reduce simply to

$$X = X_0 e^{kt} \text{ and } Y = Y_0 e^{kt}$$

and each separate component increases with time as though it were formed by the simple autocatalytic law (1).

It is of interest to note that this result holds generally when the interplay is between more than two components. For the case of three we have

$$dX/dt = \alpha Y, \quad dY/dt = \beta Z, \quad dZ/dt = \gamma X \quad . \quad . \quad . \quad . \quad (5)$$

Differentiation shows that $d^3X/dt^3 = \alpha\beta\gamma X = k^3X$, with similar expressions in Y and Z. The solutions are of the form

$$X = P_1 e^{kt} + Q_1 e^{\mu_1 kt} + R_1 e^{\mu_2 k}$$

where $P_1 + Q_1 + R_1 = X_0$ and 1, μ_1, and μ_2 are the three cube roots of unity, so that

$$\mu_1 = -\tfrac{1}{2} + i\frac{\sqrt{3}}{2} \text{ and } \mu_2 = -\tfrac{1}{2} - i\frac{\sqrt{3}}{2}$$

Evaluation of the constants gives

$$X = \tfrac{1}{3}\left(X_0 + \frac{\alpha}{k}Y_0 + \frac{\alpha\beta}{k^2}Z_0\right)e^{kt} + \tfrac{1}{3}\left(X_0 + \mu_2\frac{\alpha}{k}Y_0 + \mu_1\frac{\alpha\beta}{k^2}Z_0\right)e^{\mu_1 k} + \tfrac{1}{3}\left(X_0 + \mu_1\frac{\alpha}{k}Y_0 + \mu_2\frac{\alpha\beta}{k^2}Z_0\right)e^{\mu_2 k} \quad . \quad . \quad (6a)$$

$$Y = \tfrac{1}{3}\left(\frac{k}{\alpha}X_0 + Y_0 + \frac{\beta}{k}Z_0\right)e^{kt} + \tfrac{1}{3}\left(\mu_1\frac{k}{\alpha}X_0 + Y_0 + \mu_2\frac{\beta}{k}Z_0\right)e^{\mu_1 kt} + \tfrac{1}{3}\left(\mu_2\frac{k}{\alpha}X_0 + Y_0 + \mu_1\frac{\beta}{k}Z_0\right)e^{\mu_2 k} \quad . \quad . \quad (6b)$$

$$Z = \tfrac{1}{3}\left(\frac{k^2}{\alpha\beta}X_0 + \frac{k}{\beta}Y_0 + Z_0\right)e^{kt} + \tfrac{1}{3}\left(\mu_2\frac{k^2}{\alpha\beta}X_0 + \mu_1\frac{k}{\beta}Y_0 + Z_0\right)e^{\mu_1 kt} + \tfrac{1}{3}\left(\mu_1\frac{k^2}{\alpha\beta}X_0 + \mu_2\frac{k}{\beta}Y_0 + Z_0\right)e^{\mu_2 kt} \quad . \quad . \quad (6c)$$

From these three equations it is easily verified by substitution that the values when $t = 0$ are X_0, Y_0, and Z_0 respectively, and that the original first-order differential equations are satisfied.

When t becomes great the terms in $e^{\mu_1 kt}$ and $e^{\mu_2 kt}$ vanish. We then have constant ratios of X, Y, and Z. For example in these circumstances

$$X/Y = \left(X_0 + \frac{\alpha}{k}Y_0 + \frac{\alpha\beta}{k^2}Z_0\right)\Big/\left(\frac{k}{\alpha}X_0 + Y_0 + \frac{\beta}{k}Z_0\right) = \alpha/k$$

Also

$$X/Z = \alpha\beta/k^2$$

Once again we see that if some of the material is used to start a new system in which X_0, Y_0, and Z_0 are in this proportion, then each of the components continues to follow equation (1), the terms in $e^{\mu_1 kt}$ and $e^{\mu_2 kt}$ now vanishing throughout, since $\mu_1 + \mu_2 = -1$.

For the purpose of what is to follow later it will be convenient to give the solutions for the case of four interdependent components, namely, where

$$dX_1/dt = \alpha X_2, \; dX_2/dt = \beta X_3, \; dX_3/dt = \gamma X_4, \; dX_4/dt = \delta X_1$$

We have $d^4X_1/dt^4 = \alpha\beta\gamma\delta X_1$, where $\alpha\beta\gamma\delta = k^4$. A solution is $X_1 = A_1 e^{\rho kt}$, where ρ is one of the four fourth roots of unity. The general solutions are

$$X_1 = A_1 e^{kt} + B_1 e^{-kt} + C_1 e^{ikt} + D_1 e^{-ikt} \quad . \quad . \quad . \quad . \quad . \quad (7)$$

with corresponding expressions for X_2, X_3, and X_4. It is further found by introduction of the values for $t = 0$ that

$$\begin{aligned} A_1 &= \tfrac{1}{4}\{(X_1)_0 + (X_2)_0/a + (X_3)_0/b + (X_4)_0/c\} \\ B_1 &= \tfrac{1}{4}\{(X_1)_0 - (X_2)_0/a + (X_3)_0/b - (X_4)_0/c\} \\ C_1 &= \tfrac{1}{4}\{(X_1)_0 - i(X_2)_0/a - (X_3)_0/b + i(X_4)_0/c\} \\ D_1 &= \tfrac{1}{4}\{(X_1)_0 + i(X_2)_0/a - (X_3)_0/b - i(X_4)_0/c\} \end{aligned}$$

where $a = k/\alpha$, $b = k^2/\alpha\beta$, and $c = k^3/\alpha\beta\gamma$.

Further,

$$A_1 : A_2 : A_3 : A_4 = 1 : a : b : c,\ B_1 : B_2 : B_3 : B_4 = 1 : -a : b : -c,$$
$$C_1 : C_2 : C_3 : C_4 = 1 : ia : -b : -ic,\ D_1 : D_2 : D_3 : D_4 = 1 : -ia : -b : ic$$

Once again we find that when t is large the ratios of X_1, X_2, X_3, and X_4 become independent of time and are, in fact, $1 : a : b : c$. Each component, moreover, now follows a law of the simple form

$$(1/X_n)\mathrm{d}X_n/\mathrm{d}t = k$$

The result is, in fact, general, since if we have a system of r interlinked components we obtain a differential equation of the rth order for each, $\mathrm{d}^rX/\mathrm{d}t^r = kX$. The general solution will be the sum of r terms of the type $Ae^{\rho kt}$, where ρ is the complex rth root of unity. These rth roots form a geometrical series, and only the term in e^{kt} remains of importance when the time is sufficiently great.

The results of this section show, therefore, that non-autosynthetic enzyme systems can combine in such a way that each does in fact in the steady state increase according to the autosynthetic law.

The kinds of equation discussed probably apply with special importance to the interplay of nucleic acids and proteins in cells, each of these constituents appearing to play a decisive part in directing the synthesis of the other (cf. Malmgren and Hedén, *Acta Path. Microbiol. Scand.*, 1947, **24**, 448; Caldwell and Hinshelwood, *J.*, 1950, 3156).

Behaviour before the Steady State is reached: Lag Phenomena.—The sets of equations (4), (6), and (7) have further properties of great interest in connexion with the properties of living cells. We will first consider the case where t is small so that the steady state is not reached, and where the initial proportions of the components are arbitrary. This would correspond to the transfer of a small amount of material which had reached a steady state in one environment into another where the relevant rate constants were different and where a different steady state would finally be attained.

It will first be convenient to transform the equations of the sets (6) and (7) so as to remove the imaginary quantities, as can be done in the standard way by the introduction of the exponential values for sine and cosine. Equation (6*a*) then becomes

$$X = \tfrac{1}{3}\left(X_0 + \frac{\alpha}{k}Y_0 + \frac{\alpha\beta}{k^2}Z_0\right)e^{kt} + \tfrac{1}{3}e^{-\frac{1}{2}kt}\left\{\left(2X_0 - \frac{\alpha}{k}Y_0 - \frac{\alpha\beta}{k^2}Z_0\right)\cos\frac{\sqrt{3}}{2}kt + \sqrt{3}\left(\frac{\alpha}{k}Y_0 - \frac{\alpha\beta}{k^2}Z_0\right)\sin\frac{\sqrt{3}}{2}kt\right\} \quad . \quad . \quad (8a)$$

and equation (6*b*) becomes

$$Y = \tfrac{1}{3}\left(\frac{k}{\alpha}X_0 + Y_0 + \frac{\beta}{k}Z_0\right)e^{kt} + \tfrac{1}{3}e^{-\frac{1}{2}kt}\left\{\left(2Y_0 - \frac{k}{\alpha}X_0 - \frac{\beta}{k}Z_0\right)\cos\frac{\sqrt{3}}{2}kt + \sqrt{3}\left(\frac{\beta}{k}Z_0 - \frac{k}{\alpha}X_0\right)\sin\frac{\sqrt{3}}{2}kt\right\} \quad . \quad . \quad (8b)$$

with an analogous expression for Z.

The equations of the set (7) are similarly transformed, the value for X_1 being typical of the expressions found, *i.e.*,

$$\begin{aligned} X_1 = {} & \tfrac{1}{4}\{(X_1)_0 + (X_2)_0/a + (X_3)_0/b + (X_4)_0/c\}e^{kt} \\ & + \tfrac{1}{4}\{(X_1)_0 - (X_2)_0/a + (X_3)_0/b - (X_4)_0/c\}e^{-kt} \\ & + \tfrac{1}{4}\{2(X_1)_0 - 2(X_3)_0/b\}\cos kt + \tfrac{1}{4}\{2(X_2)_0/a - 2(X_4)_0/c\}\sin kt \quad . \quad . \quad (9a) \end{aligned}$$

The equations of the sets (8) and (9) show that until the first and major exponential term predominates the trigonometrical terms will give rise to fluctuations in the rates of increase. If, for example, we start with Y_0 and Z_0 zero in (8*a*) or with all the values save that of X_1 zero in (9*a*) then, superposed on the general exponential increase of X (or X_1) there will be a periodic variation. In the actual cases considered this effect is not very important since the amplitudes of the sine and cosine functions are small compared with the rates of increase of the terms in e^{kt}, but the principle is significant. In actual fact when a bacterial culture is prepared in one medium and a small portion of it is transferred to a completely different medium it is often a long time before growth settles down to follow the simple exponential law. In the initial stages there are often very irregular rates of increase in mass with curious bursts of growth and arrests, indicating the non-existence of a harmonious co-ordination of the various reactions involved.

Of more general importance, however, than these small-scale irregularities is the existence of a considerable lag which may precede the establishment of the steady state. This, of course, corresponds to the period of delay which is almost always observed when a bacterial culture is sampled and transferred to new surroundings.

The principle is evident from an inspection of equation (4*a*). If we start with Y_0 equal to zero then

$$X = \tfrac{1}{2}X_0(e^{kt} + e^{-kt})$$

Expansion of the exponential terms leads to the expression

$$X = X_0(1 + \tfrac{1}{2}k^2t^2 + \ldots .) \quad . \quad . \quad . \quad . \quad . \quad . \quad (10)$$

the terms in the first power of t having vanished. Thus the *initial* slope of the curve of X against t is *zero*, and there is a delay in the establishment of the normal rate of increase. The delay increases in an interesting way as the complexity of the interlocking of the various systems increases. With the three-component system we have from (8*a*) when Y_0 and Z_0 are zero

$$X = \tfrac{1}{3}X_0\left(e^{kt} + 2e^{-\frac{1}{2}kt}\cos\frac{\sqrt{3}}{2}kt\right)$$

and when the exponential and cosine terms are expanded in powers of t this gives

$$X = X_0\left(1 + \frac{1}{6}k^3t^3 + \ldots .\right) \quad . \quad . \quad . \quad . \quad . \quad . \quad (11)$$

where not only the first but also the second differential coefficient of X with respect to the time vanishes.

Equation (9*a*) with all the initial values zero save that of X_1 gives

$$X_1 = (X_1)_0\left\{1 + \frac{1}{24}k^4t^4 + \ldots .\right\} \quad . \quad . \quad . \quad . \quad . \quad (12)$$

where the first three differential coefficients vanish at $t = 0$.

From (10), (11), and (12) we can infer that for the case of n interdependent components the corresponding expression would be

$$X = X_0\{1 + (kt)^n/n! + \ldots .\} \quad . \quad . \quad . \quad . \quad . \quad . \quad (13)$$

according to which the rate would rise very slowly to its steady value when n is considerable.

The general form (13) can be derived directly as follows. With the n components we shall have differential equations of the form $d^nX/dt^n = k^nX$. The solution of this is of the type

$$X_1 = A_1e^{kt} + B_1e^{rkt} + C_1e^{r^2kt} + \ldots . Pe^{r^{n-1}kt}$$

where $1, r, r^2 \ldots r^{n-1}$ are the nth roots of unity, which are known to form a series in

geometrical progression. The constants A_1 . . . etc., are linear functions of $(X_1)_0$, etc., so that we have, when the initial values of all the components save X_1 are zero

$$X_1 = \frac{(X_1)_0}{n}\{e^{kt} + e^{rkt} + \ldots + e^{r^{n-1}kt}\}$$

The successive exponential terms can be expanded, and the coefficients of kt found. That of kt is $(1 + r + r^2 + \ldots + r^{n-1}) = (1 - r^n)/(1 - r)$ which is zero since $r^n = 1$. Similarly that of $(kt)^{n-1}$ is found to be zero. That, however, of $(kt)^n$ is

$$(1/n!)(1 + r^n + r^{2n} + \ldots + r^{(n-1)n})$$

which is

$$\frac{1}{n!}\left\{\frac{1 - (r^n)^n}{1 - r^n}\right\} = \frac{1}{n!}\left\{\frac{1 - p^n}{1 - p}\right\} = \frac{1}{n!}(1 + p + p^2 \ldots + p^{n-1}) = \frac{n}{n!}$$

since $p = r^n = 1$. Thus

$$X_1 = (X_1)_0\frac{1}{n}\left\{n + \frac{n(kt)^n}{n!} + \ldots\right\} = (X_1)_0\{1 + (kt)^n/n! + \ldots\}$$

as in (13).

The general conclusion to be drawn from the above is that the more complex the interdependence of the various processes the longer will be the time required for the establishment of the steady state where the simple exponential law of autocatalytic growth is obeyed. The presumed complexity of the interdependence in living cells readily explains the pronounced tendency for lag phases to declare themselves in the phenomena of bacterial growth. It also appeared from the earlier part of this section that when systems are badly out of adjustment more complicated irregularities such as arrests and accelerations of growth are in principle possible, though the simplified nature of the models here considered hardly does justice to the real examples encountered. A rather more specialised theory on the same general lines as the above and in which very long lags may attend the interdependence of two processes only has been given already (Hinshelwood, " Chemical Kinetics of the Bacterial Cell," Oxford, 1946, p. 82).

Cell Division and Its Introduction into Kinetic Treatments of Growth.—Living matter displays its characteristic properties essentially when organised in cells. When cells have grown beyond a certain size they normally divide. This process is a physicochemical necessity for the maintenance of approximately constant conditions of concentration, even with a standard external medium, since gains and losses from the cell depend upon its surface area while the sum of its synthetic reactions is a function of its volume. It might be thought that the kinetic treatment of cell reactions would demand a detailed hypothesis about the mechanism of cell division, but this is not so, at least for many purposes.

The cell may be imagined to divide when some structure within it exceeds a critical size for stability, or alternatively when the concentration of some active substance within it reaches a critical value. In either case the condition will be that the amount of some cellular component attains a more or less standard value. Such an assumption is strongly suggested by the finding that, for example, the amount of deoxyribose nucleic acid per cell is very nearly constant despite wide variations of growth conditions, but there is no very urgent need to specify the substance or component in question. Suppose, for example, that some concentration, c, within the cell must reach a value c_1 for division to occur. If x is the amount of the enzyme system producing this, then we shall have $dc/dt = ax - bc$, where a and b are constants in a given set of circumstances. This equation expresses the fact that the rate of loss of the active substance, whether by diffusion or by consumption in chemical change, is proportional to c. A steady state will be very rapidly set up in a cell so that $dc/dt = 0$, *i.e.*, so that $c = kx$, and the critical concentration c_1 will correspond to a critical amount x_1 per cell of the enzymic component, just as it would if the condition were an unstable critical size of this component itself.

Without, therefore, making specific assumptions about the precise mechanism of division, we may take cognisance of its occurrence and necessity in the following way. We

represent the *total* amounts, not per cell but in the whole mass of matter present, of the various constituents by X, Y, and so on. The corresponding amounts per cell are x, y, and so on, which are respectively X/n, Y/n . . . , where n is the number of cells. One of the constituents, for example Y, fills the rôle considered above, a critical value y_1 determining the division. Then we shall have y_1 which is proportional to Y/n as a constant, *i.e.*, $Y/n = \beta$.

We now have $(1/n)\mathrm{d}n/\mathrm{d}t = (1/Y)\mathrm{d}Y/\mathrm{d}t$ as an invariant condition. When a steady state prevails $(1/X)\mathrm{d}X/\mathrm{d}t = (1/Y)\mathrm{d}Y/\mathrm{d}t = \ldots$, but when it does not, as in the vitally important periods of adjustment to new environmental conditions, it is only the Y increase which is directly correlated with that of n.

This principle will be illustrated by a discussion of adaptive changes in the proportions of the components of autosynthetic systems in various circumstances.

Adaptive Phenomena.—One of the most remarkable properties of bacterial cells is their power of adapting themselves to resist the action of toxic drugs or to utilise new substrates. Without discussion of the biological aspects of these effects it will be shown that autosynthetic systems of the kind described above show these characteristics. The treatment given goes beyond that given in previous papers (Davies, Hinshelwood, and Pryce, *Trans. Faraday Soc.*, 1944, **40**, 412; Hinshelwood and Lewis, *Proc. Roy. Soc.*, 1948, *B*, **135**, 316) in dealing with the questions of the rate of adaptation, the stability of the adapted state, and the mode in which changed substrates induce the adaptive change.

(a) *Resistance to inhibitors.* In the kind of autosynthetic system present in a living cell there is a sequence of enzyme processes each dependent upon material derived from a previous one. Suppose two of the enzymes (or mutually interlocked sets of enzymes) are present in total amounts X and Y. Let the increase in Y be dependent upon the concentration of something derived from the X-set in such a way that we have the equations

$$(1/X)\mathrm{d}X/\mathrm{d}t = k_1 \text{ and } \mathrm{d}Y/\mathrm{d}t = \alpha c Y,$$

where c is the concentration in question. By the principle explained in the last section, c is proportional to the amount x_1 per cell, *i.e.*, to X/n, so that

$$\mathrm{d}Y/\mathrm{d}t = k\alpha XY/n.$$

Let Y be the constituent whose amount determines division, so that, by the principle explained above, $Y/n = y_1 = \beta$, a constant. Thus we have

$$X = X_0 e^{k_1 t} \text{ and } \mathrm{d}Y/\mathrm{d}t = k\alpha\beta X$$

whence by integration

$$Y - Y_0 = \frac{k\alpha\beta X_0}{k_1}\{e^{k_1 t} - 1\} = \frac{k\alpha\beta}{k_1}(X - X_0) \quad . \quad . \quad . \quad . \quad (14)$$

X_0 and Y_0 being the amounts at time zero.

When X and Y are large compared with X_0 and Y_0, (14) gives

$$X/Y = x_1/y_1 = k_1/k\alpha\beta = \chi$$

The ratio settles down to the constant value χ, which gives the value of X_0/Y_0, or of x_1/y_1, for a new series of observations made after a small sample of the original material is transferred to a new medium.

Suppose such a transfer is made into a medium containing an inhibitor which in some way reduces the rate of synthesis of the Y system. This means a reduction of k to k' (or an equivalent change in α). Initially the rate of synthesis of the Y system, which determines the increase in the cell number n, is reduced, since $(1/Y_0)\mathrm{d}Y/\mathrm{d}t = k'\alpha x_1$, which is less than the previous value in the ratio k'/k. After continued growth in the new conditions, however, x_1 increases to x_1', since x_1/y_1 changes to χ' which is $k_1/k'\alpha\beta$, and y_1 by hypothesis is invariant. Thus x_1' is finally greater than x_1 in the same ratio as k' is less than k. Thus the final value after continued growth is $(1/Y)\mathrm{d}Y/\mathrm{d}t = k'(k/k')\alpha x_1$,

which is the original value once more. There is thus an adaptive change in the cell proportions which makes the final multiplication rate independent of the inhibitor.

Whenever the stable ratio of X to Y is established, it follows from (14) that $(1/n)\mathrm{d}n/\mathrm{d}t = (1/Y)\mathrm{d}Y/\mathrm{d}t = k_1 = (1/X)\mathrm{d}X/\mathrm{d}t$.

Examples of the complete adaptation of a bacterial culture to resist an inhibitory drug are quite common, and will not be discussed here, the present object being the establishment of the principles by which the kinetic calculations can be made.

(b) *Rate of development of resistance.* We transfer a sample of the material where $X/Y = \chi$ to a new medium where, since k' is less than k, the initial rate of growth is slower, and where the final stable value of X/Y will have to rise to χ' before adaption is complete. X_0/Y_0 will be χ, and *not* χ'. From (14) we have

$$\frac{X}{Y} = \frac{X_0 e^{k_1 t}}{Y_0 + \frac{k'\alpha\beta}{k_1}\{e^{k_1 t} - 1\}}$$

$$= \frac{\chi e^{k_1 t}}{1 + \frac{\chi}{\chi'}\{e^{k_1 t} - 1\}} \quad \text{since } X_0 = \chi Y_0 \quad . \quad . \quad . \quad . \quad . \quad (15)$$

When $t = 0$ this expression is χ, and when t is infinite it is χ'. The ratio approaches its limiting value, however, as soon as $e^{k_1 t}$ becomes substantially greater than unity. This means that a very considerable degree of adaptation occurs quite rapidly. The completion of the process, however, may require a much longer, and in theory an infinite, time.

This result corresponds to what is observed, where the initial stages of adaptive processes are often very rapid, but their completion may demand a great number of subcultures of the organism in the new medium.

(c) *Stability of resistance to inhibitors.* This is a complex problem, and has hitherto occasioned some difficulty in its interpretation.

Stability is judged in the following way. The growing material is adapted to a new medium (containing the inhibitor) : a sample of it is then re-transferred to the original medium where further growth is allowed to take place for a determined time. The material is then tested once more for its growth rate in the medium containing the inhibitor. To varying degrees it displays an apparent memory for its previously induced power to resist the action of the adverse environment. The complete picture of the behaviour is rather a complex one. Sometimes the reversion to the unadapted state is rapid, sometimes very slow. We shall now consider the explanation of these phenomena in terms of the model which has been developed.

According to equation (15), the re-transfer of adapted material to its original environment would result in a change of χ back to the old value at about the rate of the forward change. Thus, further tests in presence of inhibitor would show that a rapid reversion had taken place. This, in fact, is what is often observed with bacterial cultures which have just become nearly but not very thoroughly adapted to a changed environment, so that to this extent the prediction of the model system corresponds to the reality.

But there is often a state of what may be termed metastable adaptation where the material preserves its newly acquired property through many generations of culture in the original medium removed from the inducing agent, displaying, as it were, memory of its first training. This happens usually only when the initial process of adaptation has been carried on for a long time and reached completion.

(d) *Slowness of reversion.* To account for this we must reconsider a previous assumption, namely, that the rate of functioning of the Y-enzyme in section (a) is directly proportional to the concentration, c, of the active intermediate derived from the enzyme system which supplies it. In general, the rate will be governed by an adsorption isotherm, and should be set proportional, not simply to c, but to $c/(a + c)$, *i.e.*, should follow a Langmuir isotherm, or some similar equation. This expression gives simple proportionality to c when c is small, but becomes independent of it when c is great enough.

Now the two cases of adaptation to the inhibitor and reversion to the original state in its absence differ in one important respect. In the adaptive process c will have been reduced to a low value and gradually returns to a normal value. Thus it is quite reasonable to assume, as has been done so far, that the rate of functioning of the Y-system is directly proportional to c. In the reversion, x_1 and, therefore, c start at a greatly enhanced value for the original medium and should gradually fall. But when c is great, the enzyme system Y may well be nearly saturated with the intermediate, so that the rate of formation of Y does not show any marked increase. In such circumstances reversion may be very slow. As an approximate representation of the adsorption isotherm function $c/(a + c)$ when c is great we may write proportionality to $c^{1/p}$, where p is a number greater than unity. The nearer to saturation, the greater will be the effective value of p.

The rate of functioning of the Y-enzyme system will now be proportional, not to x_1, but to $(x_1)^{1/p}$, and the equations of sections (a) and (c) assume the following forms :

$$\begin{aligned} \mathrm{d}Y/\mathrm{d}t &= k\alpha x_1^{1/p} Y = k\alpha X^{1/p} Y/n^{1/p} = k\alpha X^{1/p}(Y/n)^{1/p} Y^{1-1/p} \\ &= k\alpha\beta' X^{1/p} Y^{1-1/p}, \text{ where } \beta' = (Y/n)^{1/p} \\ \mathrm{d}X/\mathrm{d}t &= k_1 X \end{aligned}$$

whence by integration we obtain a modified form of equation (14), namely,

$$\frac{X}{Y} = \frac{(X_0/Y_0)\mathrm{e}^{k_1 t}}{\left\{1 + \frac{k\alpha\beta'}{k_1}\left(\frac{X_0}{Y_0}\right)^{1/p}(\mathrm{e}^{k_1 t/p} - 1)\right\}^p} \quad . \quad . \quad . \quad . \quad . \quad . \quad (16)$$

When t is very great this expression assumes the value $(k_1/k\alpha\beta')^p = \chi_1$.

If the material has undergone an adaptive change, χ_1 will change to a new value χ_1' and the reversion from the latter to the former on re-transfer to the original medium will be governed by equation (16) with $X_0/Y_0 = \chi_1'$, *i.e.*, $(k_1/k'\alpha\beta')^p$. Thus we shall have

$$\frac{X}{Y} = \frac{\chi_1' \mathrm{e}^{k_1 t}}{\left\{1 + \left(\frac{\chi_1'}{\chi_1}\right)^{1/p}(\mathrm{e}^{k_1 t/p} - 1)\right\}^p} \quad . \quad . \quad . \quad . \quad . \quad . \quad (17)$$

For the reversion to be appreciable $\mathrm{e}^{k_1 t/p}$ must now considerably exceed unity, and if p is great enough this may require very large times indeed, for in the limit, where the active intermediate produced by X entirely saturates Y in normal conditions, p approaches infinity and the reversion becomes infinitely slow.

Approaches to this case are actually encountered. Sometimes, adapted bacterial cultures survive hundreds of generations in their original medium without losing the power of rapid growth in a second medium to which they had become acclimatised. But their state is essentially not one of true stability since reversion usually occurs in the long run, or may be induced by special means.

(e) *Dependence of reversion on the thoroughness of the previous adaptation.* The following typical set of facts illustrates the problem to be considered. If certain bacteria have just been adapted to resist a drug, then cultivation in the absence of the drug causes rapid loss of resistance, as shown in further tests with the drug restored to the medium. If, however, the adaptation has been long continued, then the resistance is more nearly permanent. It is not the object of this paper to discuss alternative biological explanations of this behaviour, but to show in what circumstances the kinetic model under investigation would predict it.

We still envisage the two-enzyme systems X and Y of the previous paragraphs. By the equations already given we have

$$\mathrm{d}X/\mathrm{d}t = k_1 X \text{ and } \mathrm{d}Y/\mathrm{d}t = \alpha c Y = k_2 Y$$

For a steady state $k_1 = k_2$: otherwise the ratio of X to Y changes, and at a rate which depends upon the difference between k_1 and k_2. The amount of X per cell, x_1, adjusts itself in the process of adaptation as has been shown. If αc is lowered by any agency then,

as shown, x_1 increases and causes a rise in c which in turn increases k_2 till k_1 and k_2 can once more be equal. Suppose in the normal state the Y-system is nearly but not quite saturated with the intermediate, and suppose that the inhibitor somehow interferes with the supply and reduces c. Adaptation raises c from the lowered value c' to the normal value c, *i.e.*, from well below the value required to saturate the Y-system nearly to this value again. The Y-system responds. Now if the inhibitor is removed, the increased proportion of x_1 raises c to a new value c'', which corresponds more nearly to saturation than did the original value c. Thus k_2 now exceeds k_1, and the ratio of X/Y regresses, *i.e.*, reversion occurs. But the process may be quite slow (see last section) if we are near enough to saturation for the increase in k_2 to be small.

So far we have considered two consecutive sets of enzymes, but cells are much more elaborate organisations. Although we have assumed αc to suffer the main effect of the inhibitor, the relations of all sorts of other cell processes may have been affected in a secondary degree, and in the course of adaptation numerous secondary adjustments are likely. Suppose now that, although the main effect of the inhibitor is on k_2, yet k_1 also suffers some small reduction. The adaptive change which leads to the restoration of k_1 can be very slow, partly because the reduction in any case is not great. In the meantime k_2 can rise, not to k_1, but to this lowered value k_1'. Presently, however, k_1 is restored to its initial value, and may now rise to a still higher value k_1'' on return to the normal conditions. Since k_2 was in any case near to its saturation value, an extremely small increase in k_1'' will be sufficient to balance the increase which has occurred in k_2'', and to convert a moderate rate of reversion into an extremely slow one.

There are other possibilities depending upon the complicated interlocking of cell processes, but they will not be further discussed here.

(f) *Adaptation to new substrates.* Bacterial cells are capable of utilising fairly varied sources of carbon, though the compounds which will support growth are not usually wholly unrelated. Glucose and many other sugars form one of the main groups, and the other consists of the series of breakdown products derived from glucose, namely, glyceraldehyde and its derivatives, pyruvic acid, and various acids of the dicarboxylic and tricarboxylic acid series which are connected in a definite metabolic pattern (Krebs cycle and its variants).

It is a fundamental question whether in the adaptation to utilise a new substrate existing enzymes are used in changed proportions, so that their previous ratios in the cell are quantitatively altered, or whether existing enzymes undergo qualitative alteration. An outline of the theory of the first type of process has already been given (Hinshelwood, *op. cit.*, p. 180; Hinshelwood and Lewis, *loc. cit.*), and the second type has been dealt with in a qualitative way only. It is proposed here to develop a view which is a synthesis of both these alternatives, and which links together all the preceding parts of the present paper.

We have already envisaged the autosynthetic system as consisting of interlocking parts, *e.g.*, a certain type of nucleic acid which guides the formation of a certain type of protein and vice versa. The relevant equations are

$$\mathrm{d}R/\mathrm{d}t = A_1P_1 \text{ and } \mathrm{d}P_1\mathrm{d}t = B_1R \quad . \quad . \quad . \quad . \quad . \quad . \quad (18)$$

where R is the amount of the nucleic acid, and P_1 that of the protein, A_1 and B_1 being constants. (The specific identification of R and P_1 as nucleic acid and protein is of course not essential, but illustrative: what matters is the interlocking system.)

Now let it be supposed that the protein P_1 constitutes the enzyme (enzyme X of the previous paragraphs) which by interaction with a substrate S_1 gives an intermediate (concentration c_1) which in turn is used by the enzyme system Y, where Y, as before, is the critical division-determining component.

As previously shown, in the steady state (18) leads to $R = R_0e^{k_1t}$, $P_1 = (P_1)_0e^{k_1t}$ where $k_1^2 = A_1B_1$ and $R/P_1 = (A_1/B_1)^{\frac{1}{2}}$. As in section (a) we have also

$$\mathrm{d}Y/\mathrm{d}t = \alpha c_1Y = k\alpha x_1Y = k\alpha XY/n = k\alpha P_1Y/n = k\alpha\beta P_1$$

Then as in (14) we have

$$Y - Y_0 = (k\alpha\beta/k_1)\{P_1 - (P_1)_0\} \quad . \quad . \quad . \quad . \quad . \quad (19)$$

In the steady state $P_1/Y = k_1/k\alpha\beta$ and $R/Y = A_1/k\alpha\beta$, since $k_1 = (A_1B_1)^{\frac{1}{2}}$. The growth rate constant $(1/n)\mathrm{d}n/\mathrm{d}t = (1/Y)\mathrm{d}Y/\mathrm{d}t = (1/R)\mathrm{d}R/\mathrm{d}t = k_1$.

When growth occurs in the substrate S_2 we must suppose that a different enzyme-protein, P_2, is involved, and that this leads to the formation from the new substrate, in one or more stages, of the intermediate required for Y. We shall now have

$$\mathrm{d}Y/\mathrm{d}t = \alpha c_2 Y = k'\alpha\beta P_2,$$

c_2 and k' being different from c_1 and k, respectively.

In the new steady state, R will attain the value given by $R/Y = A_2/k'\alpha\beta$, so that $R_{S_2}/R_{S_1} = A_2k/A_1k'$. If A_2 and A_1 are not very different, *e.g.*, if the two proteins P_1 and P_2 are about equally efficient in guiding the nucleic acid formation, but if k' is much less than k, *i.e.*, if the new substrate is a much less efficient source of the required intermediate, then, just as in the case of the inhibitor action, the response of the cell is an expansion of the basic formative structure R. Until this has occurred the growth rate remains below its optimum k_1'.

For the steady states we have then

$$R_{S_1}/P_1 = (A_1/B_1)^{\frac{1}{2}} \text{ and } R_{S_2}/P_2 = (A_2/B_2)^{\frac{1}{2}}$$

and

$$R_{S_1}/Y_{S_1} = A_1/k\alpha\beta \text{ and } R_{S_2}/Y_{S_2} = A_2/k'\alpha\beta$$

The maximum growth rate constants for the two substrates are $k_1 = (A_1B_1)^{\frac{1}{2}}$ and $k_1' = (A_2B_2)^{\frac{1}{2}}$. The R/P ratios are determined only by A and B and are unaffected by k or k'. On the other hand, the ratio of R and P themselves to Y depends upon k or k' and settles down to a greater value the smaller these constants are. The optimum degree of adaptation is determined therefore by A and B only. If their product is small, no amount of adaptive response will increase the growth rate beyond what they allow. If, on the other hand, their product is large but k' is very small, the initial rate on transfer to the new substrate will be small but can rise to a high value in time. This kind of behaviour is in fact found. *Bact. lactis aerogenes* when first transferred from glucose to D-arabinose shows a very long lag but finally attains a growth rate comparable with but still less than that in glucose.

The lag on transfer from S_1 to S_2 is roughly calculable as follows. In equations (4*a*) and (4*b*), X becomes R, Y becomes P_2, $Y_0 = (P_2)_0 = 0$, $\alpha = A_2$, and $\beta = B_2$; k is k_1'. Then

$$P_2 = (\tfrac{1}{2}k_1'R_0/A_2)(\mathrm{e}^{k_1't} - \mathrm{e}^{-k_1't})$$

so that

$$\begin{aligned}\mathrm{d}Y/\mathrm{d}t = k'\alpha\beta P_2 &= (\tfrac{1}{2}k'k_1'\alpha\beta R_0/A_2)(\mathrm{e}^{k_1't} - \mathrm{e}^{-k_1't}) \\ &= (\tfrac{1}{2}k'k_1'\alpha\beta R_0/A_2)(2k_1't) \text{ approx. for small changes.}\end{aligned}$$

Since $Y = \beta n$, we have for the early stages

$$(1/n)\mathrm{d}n/\mathrm{d}t = k'(k_1')^2(\alpha/A_2)(R_0/n)t \quad . \quad . \quad . \quad . \quad . \quad . \quad (20)$$

The definitition of the lag, L, is necessarily somewhat arbitary, but if we take it here as the time at which $(1/n)\mathrm{d}n/\mathrm{d}t$ begins to assume some assigned value Δ, then, since at the start $R/Y = A_1/k\alpha\beta = R_0/\beta n$,

$$\begin{aligned}L &= \Delta(A_2/\alpha)(n/R_0)\{1/k'(k_1')^2\} \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad (21) \\ &= \Delta(1/k_1')^2(k/k')(A_2/A_1) \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad (22)\end{aligned}$$

Equation (22), which makes the lag independent of R_0 in appearance, assumes of course that R_0 has the equilibrium value corresponding to S_1. If k' is small, in particular, the lag is long.

(g) *Stability and reversion of substrate adaptation.* As in the case of drug resistance, the equations so far given predict rapid adaptation and rapid reversion on transfer between two media containing S_1 and S_2 respectively. This is sometimes observed, but often the adaptation is rather stable.

Once again it is necessary to reconsider the tacit assumption that the rate of synthesis of enzyme Y is directly proportional to the concentration c. This assumption leads to

(19). If enzyme Y becomes saturated, the rate cannot rise above a limit. Suppose now we first effect equilibration in substrate S_1 where R/Y reaches a definite value, and then transfer to S_2 where k' is very small, so that R/Y expands greatly. Now re-transfer to S_1. The amounts of R and presently of P_1 per cell will be abnormally great. If there is a linear relation of dY/dt to c, Y will expand again relatively to R and P_1 and the old ratio will be restored. If, however, Y was already saturated in the normal functioning in S_1, the rise in c will produce no response. The values of $(1/R)dR/dt$ and of $(1/Y)dY/dt$ will be k_1, and the second will not rise above it. Hence the abnormal proportions will be preserved, and will give the cells an abiding advantage if at a later stage they are yet again transferred to S_2, since in (21) R_0/n will have, not the value there calculated, but an abnormally great value. This circumstance will not, however, abolish all the lag, since P_2 has in any case to be formed. The lag will, however, be less than it would have been had the previous adaptation not occurred.

That in a common substrate like glucose the enzyme Y may often be working at near saturation is quite possible, since this point would be precisely that at which adaptive processes of other kinds in S_1 would have reached the limit of their effectiveness.

It is not suggested that the mechanisms here discussed in any way exhaust the possibilities for the explanation of the varied phenomena of adaptation to new substrates.

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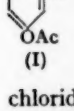
137. *Acylation Reactions Catalysed by Strong Acids. Part VI.* A Comparison of Zinc Chloride and Perchloric Acid as Catalysts for the Thiele Acetylation of Quinones.*

By H. BURTON and P. F. G. PRAILL.

Zinc chloride is not an effective catalyst for the general reaction named in the title; mixtures of the normal triacetates and chlorodiacetates are usually produced. Tolu-2 : 5-quinone gives mainly an abnormal chlorotoluquinol diacetate. The simpler quinones react rapidly with acetic anhydride in the presence of a little 72% perchloric acid. 2-Methyl-1 : 4-naphthaquinone also undergoes the reaction under suitable conditions; a synthesis of phthiocol is thus available.

IN their initial work on the reaction which is now generally known as " the Thiele acetylation of quinones," Thiele and Winter (*Annalen*, 1900, **311**, 341) used, for the most part, a solution of the quinone in an excess of acetic anhydride containing a little concentrated sulphuric acid. It has been pointed out by us (*J.*, 1950, 1203), and confirmed by Gillespie (*J.*, 1950, 2997), that acetylium ions would be produced from the acetic anhydride–sulphuric acid mixture. Thiele and Winter also used, to a limited extent, a mixture of zinc chloride † and acetic anhydride but obtained chloroquinol diacetate (I) from benzoquinone, and 1 : 2 : 4-triacetoxynaphthalene from either 1 : 2- or 1 : 4-naphthaquinone. We have also shown (*J.*, 1951, 726) that mixtures of zinc chloride and an excess of acetic anhydride are sources of acetylium ions, and the above result with benzoquinone might appear to be anomalous, since the formation of (I) involves, in the first instance, the addition of acetyl chloride (not necessarily as such).



(I)

It has long been stated (Schulz, *Ber.*, 1882, **15**, 652) that benzoquinone and acetyl chloride react in the absence of any catalyst to give a mixture of quinol diacetate (I) and 2 : 5-dichloroquinol diacetate, but no yields of these products were given.

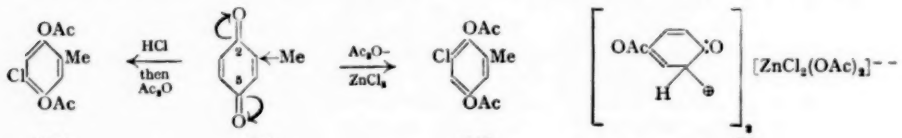
We have reinvestigated the reaction between benzoquinone and acetic anhydride–zinc chloride and find that when mixtures containing more than 2 mols. of the anhydride

* Part V, *J.*, 1951, 726.

† Although zinc chloride is usually referred to as a catalyst for the Thiele acetylation, it is actually used in approximately the same molecular amount as the quinone.

are heated an exothermic reaction occurs; after a short time zinc acetate crystallises from the reaction mixture but in no case was there any evolution of hydrogen chloride. In all the experiments we carried out we had no difficulty in isolating some 1 : 2 : 4-triacetoxybenzene in addition to (I); the amount varied according to the experimental conditions.

Thiele and Winter (*loc. cit.*) showed that tolu-2 : 5-quinone (II) gave a high yield of



(IV) (II) (III) (V)

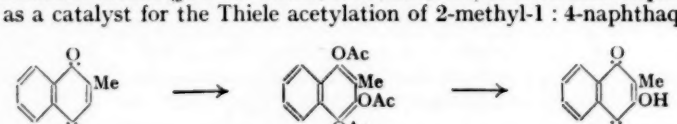
2 : 4 : 5-triacetoxytoluene with acetic anhydride–sulphuric acid. With acetic anhydride–zinc chloride we have found that a little of the triacetate, and a relatively large amount of 3-chlorotolu-2 : 5-quinol diacetate (III), m. p. 65°, are produced. The production of (III) appeared to us to be abnormal since the electronic displacements in (II) suggest that the normally orientated chlorotoluquinol diacetate should be the 4-chloro-isomer (IV). As with benzoquinone, we found that zinc acetate separated from the hot reaction mixture and that no volatile product was evolved.

The structure of (III) follows from its hydrolysis to 3-chlorotolu-2 : 5-quinol, m. p. 113—114°, the constitution of which was established by Angeletti and Oliverio (*Gazzetta*, 1940, **70**, 342). 4-Chlorotolu-2 : 5-quinol, m. p. 175°, has been prepared by the addition of hydrogen chloride to (II) (Schniter, *Ber.*, 1887, **20**, 2285; Clark, *J. Amer. Chem. Soc.*, 1892, **14**, 574; Raiford, *Amer. Chem. J.*, 1911, **46**, 450) and its constitution was established by Raiford. We find that its diacetate (IV) has m. p. 112—113°.

The reaction (II) ⟶ (III) would appear to necessitate the addition of an acetylium ion to the $C_{(5)}$:O of (II) with the intermediate production of the complex (V) and in this sense the reaction can be considered to be abnormal. It is known (Part V, *J.*, 1951, 726) that acetylium ions are produced from mixtures of zinc chloride and an excess of acetic anhydride; since no hydrogen chloride is evolved during the reaction, we must presume that the complex (V) decomposes to zinc acetate and the necessary chloro-acetoxy-intermediate. We are of the opinion that complexes of type (V), which are in fact ternary, are probably more important in reactions involving Friedel–Crafts catalysts than has hitherto been generally realised.

We have also reinvestigated the reaction of 1 : 4-naphthaquinone with zinc chloride–acetic anhydride and find, in agreement with Thiele and Winter (*loc. cit.*), that 1 : 2 : 4-triacetoxynaphthalene is the major product; we have however been able to show that a little of a chlorine-containing compound—presumably 1 : 4-diacetoxy-2-chloronaphthalene—is also produced.

Anderson and Newman (*J. Biol. Chem.*, 1933, **103**, 405) showed that sulphuric acid was ineffective as a catalyst for the Thiele acetylation of 2-methyl-1 : 4-naphthaquinone (VI).



(VI) (VII) (VIII)

We have shown that (VI) is equally resistant to the action of zinc chloride–acetic anhydride: in the experiments we have carried out, provided that extensive decomposition did not occur, we recovered a very high proportion of unchanged quinone. In analogous experiments using nitromethane as the solvent we were able to isolate a very small amount of a chlorine-containing substance which we believe to be 1 : 4-diacetoxy-3-chloro-2-methylnaphthalene and which must be formed by a mechanism similar to that discussed above.

The kinetic study by Mackenzie and Winter (*Trans. Faraday Soc.*, 1948, **44**, 171, 243) of the perchloric acid-catalysed Thiele acetylation of benzo- and tolu-quinones shows clearly that this acid is a very effective catalyst. Our results (*J.*, 1950, 1203) on the *C*-acetylation of anisole with acetic anhydride–perchloric acid, in conjunction with those of Mackenzie and Winter, indicate that if acetylium ions alone are the " driving force " for the Thiele acetylation process then it should be possible to effect the reaction (VI) ⟶ (VII); at the same time it must be emphasised that an excess of acetic anhydride is a necessary factor. We have found, as briefly reported earlier (*Chem. and Ind.*, 1950, 92), that, provided that a relatively large amount of perchloric acid is used, (VII) can be obtained in yields of 43—54% after 20 hours at room temperature. In marked contrast to this result, we find that 1 : 4-naphthaquinone and benzo- and tolu-quinone (cf. Mackenzie and Winter, *locc. cit.*) are rapidly converted by a little 72% perchloric acid and an excess of acetic anhydride into almost quantitative yields of the appropriate triacetoxy-derivatives.

There appears little doubt that for preparative purposes perchloric acid is probably the most efficient catalyst for the Thiele acetylation. It would seem however from the work of Fieser (*J. Amer. Chem. Soc.*, 1948, **70**, 3165) and Cram (*ibid.*, 1949, **71**, 3953) that boron trifluoride is also an efficient catalyst, presumably because of the facile reaction $Ac_2O + BF_3 \longrightarrow Ac^+ + [BF_3{\cdot}OAc]^-$.

Alkaline hydrolysis of (VII) with free access to air gave as expected a high yield of 3-hydroxy-2-methyl-1 : 4-naphthaquinone (phthiocol) (VIII) thus affording a simple synthesis of this important compound (Anderson and Newman, *J. Biol. Chem.*, 1933, **101**, 773).

Experimental

Reactions with acetic anhydride and zinc chloride.

Benzoquinone.—(*a*) The quinone (10·2 g.) rapidly dissolved on addition to a solution of zinc chloride (16·2 g.) in acetic anhydride (24·0 g.); the mixture was then heated on a steam-bath, whereupon a slight exothermic reaction occurred and the internal temperature rose to 100°. Gentle heating was continued for 1 hour and during the latter half of this period a considerable amount of zinc acetate separated. The cooled mixture was poured into water and after several hours the semi-solid product was filtered off and dissolved immediately in hot methanol. The first crop of crystalline material obtained was almost pure chloroquinol diacetate (8·8 g.), pale orange rhombic prisms (from benzene–light petroleum), m. p. 72°. A further crop of crystalline material (1·2 g.) gave colourless needles, m. p. 96—97°, from alcohol, which did not depress the m. p. of 1 : 2 :4-triacetoxybenzene.

A considerable amount of non-crystallisable gummy material was isolated from the mother-liquors.

(*b*) A solution of benzoquinone (0·08 g.-mol.) and zinc chloride (0·01 g.-mol.) in acetic anhydride (0·40 g.-mol.) was heated on a boiling water-bath for 6 hours. During this period the mixture darkened and separation of zinc acetate occurred. The cooled mixture was poured into water, and the product was worked up as in (*a*), giving chloroquinol diacetate (0·007 g.-mol.) and 1 : 2 : 4-triacetoxybenzene (0·004 g.-mol.). An ethereal extract of the aqueous liquor yielded some tar.

(*c*) The same mixture as for (*b*) was boiled for 30 minutes. Fractional crystallisation of the product gave chloroquinol diacetate (0·005 g.-mol.) and 1 : 2 : 4-triacetoxybenzene (0·005 g.-mol.) together with a dark brown gum (4·6 g.).

Tolu-2 : 5-quinone.—A solution of the quinone (0·1 g.-mol.) and zinc chloride (0·12 g.-mol.) in acetic anhydride (0·25 g.-mol.) was heated on a boiling-water-bath, the internal temperature rising to *ca.* 120°. The mixture was shaken without further heating for 10—15 minutes, by which time much solid had separated and the temperature had fallen to 95°. The mixture was then heated at 90—95° for a further 30 minutes, cooled, and poured into ice-water (*ca.* 250 c.c.). After several hours the rather waxy solid was filtered off and dissolved in the minimum amount of hot alcohol. The cooled solution deposited almost colourless needles (11·0 g.), m. p. 61°, which consisted mainly of 2 : 5-*diacetoxy*-3-*chlorotoluene*, colourless prisms (from benzene), m. p. 65° (Found : C, 54·3; H, 4·5; Cl, 15·1. $C_{11}H_{11}O_4Cl$ requires C, 54·4; H, 4·5; Cl, 14·6%), together with a little 2 : 5-diacetoxy-4-chlorotoluene, m. p. and mixed m. p. 112—113° (see below).

The residue (*ca.* 11 g.) obtained by evaporation of the alcoholic mother-liquors was a viscous

brown syrup from which further crops of crystalline material were obtained with considerable difficulty. One crop was slightly impure 2 : 5-diacetoxy-3-chlorotoluene and a further crop (3·3 g.), m. p. 54—55°, on crystallisation from benzene–light petroleum deposited hard nodules (0·6 g.), m. p. 111°, which depressed the m. p. of 2 : 5-diacetoxy-4-chlorotoluene to 90°, but admixed with 2 : 4 : 5-triacetoxytoluene had m. p. 112°.

1 : 4-*Naphthaquinone.*—(*a*) A solution of the quinone (0·02 g.-mol.) and zinc chloride (0·02 g.-mol.) in acetic anhydride (0·12 g.-mol.) was heated to 50°. At first the heat of reaction was sufficient to keep the temperature at 50° but later further heating was necessary. After 30 minutes the cooled, green reaction mixture was poured into cold water, and the precipitated yellow solid filtered off and recrystallised from methanol without drying. The crystalline material (4·3 g.) was fractionally crystallised from benzene and was shown to be a mixture of 1 : 2 : 4-triacetoxynaphthalene (1·9 g.), m. p. and mixed m. p. 130—131°, and unchanged 1 : 4-naphthaquinone.

(*b*) A similar experiment was carried out at 90° for 4 hours and here the initial dark green reaction mixture turned brown but no separation of solid material was observed. The crude product was fractionally crystallised from methanol, giving (i) light brown needles (3·0 g.), m. p. and mixed m. p. 131—132° after recrystallising from alcohol, and (ii) a mixture (2·1 g.) containing dark brown prisms, m. p. 130° (separated by hand-picking), which depressed the m. p. of 1 : 2 : 4-triacetoxynaphthalene to *ca.* 110°. These prisms which contained chlorine were dissolved in hot benzene and light petroleum (b. p. 60—80°) was added; the resulting precipitate of amorphous material was filtered off and the solution was concentrated; on cooling, hemispherical clusters of needles separated. Recrystallised from light petroleum containing a little benzene, almost colourless needles, m. p. 134—135° (Found: C, 60·2; H, 4·2; Cl, 12·8. $C_{14}H_{11}O_4Cl$ requires C, 60·3; H, 3·9; Cl, 12·7%), of presumably 1 : 4-*diacetoxy*-2-*chloronaphthalene* were obtained.

(*c*) In another experiment a similar mixture in nitromethane (24·4 g.) was heated at 85° for 2 hours. After decomposition of the reaction mixture with water the product was extracted with ether. The ethereal extract was washed with water, dried (Na_2SO_4), and evaporated in a vacuum. Fractional crystallisation of the residue gave 1 : 2 : 4-triacetoxynaphthalene (3·3 g.), m. p. and mixed m. p. 135° after recrystallisation from alcohol, and gummy material (1·8 g.).

2-*Methyl*-1 : 4-*naphthaquinone.*—(*a*) A mixture of the quinone (0·05 g.-mol.), zinc chloride (0·05 g.-mol.), and acetic anhydride (0·3 g.-mol.) was heated on a steam-bath until all the zinc chloride had dissolved (*ca.* 15 minutes) and then for a further 30 minutes. The dark mixture was cooled rapidly and decomposed with ice, whereby a light brown solid product separated. Crystallisation of this from methanol gave unchanged quinone (m. p. and mixed m. p.).

(*b*) When the above mixture was boiled under reflux for 1¾ hours, hydrogen chloride was evolved but acetyl chloride could not be detected. The reaction product was a black tar.

(*c*) A mixture of 2-methyl-1 : 4-naphthaquinone (0·05 g.-mol.), zinc chloride (0·05 g.-mol.), acetic anhydride (0·15 g.-mol.), and nitromethane (30·6 g.) was heated on the steam-bath for 8 hours; no evolution of hydrogen chloride occurred. The residue left after removal of volatile products by evaporation in a vacuum was mixed with powdered ice, and the crude solid crystallised from methanol. The first (main) crop consisted (m. p. and mixed m. p.) of unchanged quinone, but the more soluble fraction had m. p. *ca.* 95°. Recrystallisation of this from 2 : 1 benzene–light petroleum gave pale brown needles (0·1 g.), m. p. 194° after sintering at 185°. Recrystallisation from ethyl alcohol then gave colourless needles, m. p. 196—197°, of 1 : 4-diacetoxy-3-chloro-2-methylnaphthalene (Found: C, 61·9; H, 4·8; Cl, 11·8. Calc. for $C_{15}H_{13}O_4Cl$: C, 61·5; H, 4·4; Cl, 12·1%). Fries and Lohmann (*Ber.*, 1921, **54**, 2921) give m. p. 194°.

Reactions with acetic anhydride and 72% perchloric acid.

Benzoquinone.—72% Perchloric acid (0·5 c.c., 0·006 g.-mol. of $HClO_4$) was slowly added to a solution of benzoquinone (0·05 g.-mol.) in acetic anhydride (50 c.c.). The temperature rose rapidly to *ca.* 55°, and after being cooled to below 20° the mixture was left at room temperature for 30 minutes before being poured into ice-water. The slightly impure 1 : 2 : 4-triacetoxybenzene (0·048 g.-mol.), m. p. 94°, separated from methanol in colourless needles, m. p. 97·5°.

1 : 4-*Naphthaquinone.*—72% Perchloric acid (0·6 g.) was added to a solution of 1 : 4-naphthaquinone (5 g.) in acetic anhydride (30 c.c.) at room temperature. After 30 minutes the mixture was decomposed by ice-water, and the resulting solid (yield 95%), m. p. 133·5—134·5°, crystallised

from alcohol. The triacetate, m. p. 135°, was identical (m. p. and mixed m. p.) with that prepared by reductive acetylation of 2-hydroxy-1 : 4-naphthaquinone (lawsone).

2-Methyl-1 : 4-naphthaquinone.—72% Perchloric acid (0·01 g.-mol.) was added dropwise to a solution of 2-methyl-1 : 4-naphthaquinone (0·02 g.-mol.) in acetic anhydride (34·4 c.c.), and the mixture kept for 20 hours at room temperature. The resulting deep red-brown solution was poured cautiously on crushed ice (*ca.* 250 g.), and the resulting light-coloured solid product was collected and dissolved in the minimum amount of hot methanol. The solid which separated on cooling, when recrystallised from benzene–light petroleum (2 : 1), separated in clusters of colourless prisms (*ca.* 54%), m. p. 158—159° (Found : C, 64·3; H, 5·1. Calc. for $C_{17}H_{16}O_6$: C, 64·6; H, 5·1%). Anderson and Newman (*J. Biol. Chem.*, 1933, **103**, 197) give m. p. 158—159° after fusing (? sintering) at 148°, for 1 : 3 : 4-triacetoxy-2-methylnaphthalene.

With a ratio of quinone to perchloric acid of 3 : 1 the yield of pure triacetate, under otherwise identical conditions, was 43%.

3-Hydroxy-2-methyl-1 : 4-naphthaquinone (*Phthiocol*).—Hydrolysis of the above triacetate with hot 2N-sodium hydroxide and free access to air gave 80% of crude 3-hydroxy-2-methyl-1 : 4-naphthaquinone. Crystallisation from methanol gave bright yellow needles, m. p. 173° (Found : C, 70·1; H, 4·4. Calc. for $C_{11}H_8O_3$: C, 70·0; H, 4·3%). Anderson and Newman (*ibid.*, 1933, **101**, 773) give m. p. 173—174° for the natural product.

3-Chlorotolu-2 : 5-quinol.—A mixture of the diacetate (2 g.), N-sulphuric acid (5 c.c.), and alcohol (7 c.c.) was boiled for 9—10 hours; the ethyl acetate formed was allowed to evaporate from time to time, being replaced by sufficient acid–alcohol to maintain a clear solution. On cooling, colourless needles (1·0 g.), m. p. 112°, separated (Found : C, 53·1; H, 4·6; Cl, 21·9. Calc. for $C_7H_7O_2Cl$: C, 53·0; H, 4·5, Cl, 22·4%).

The quinol was readily oxidised by acid–dichromate to the quinone, which crystallised from alcohol in bright yellow needles, m. p. 90°.

4-Chlorotolu-2 : 5-quinol.—Dry hydrogen chloride was passed slowly into a solution of tolu-2 : 5-quinone (0·1 g.-mol.) in chloroform (100 c.c.) at room temperature (water-cooling) for 1 hour during which solid material separated. After the mixture had been kept for a further hour the solid (*A*) was filtered off and crystallised first from benzene–ethyl acetate (5 : 1) and then from chloroform–ethyl acetate, giving colourless prisms (0·08 g.-mol.), m. p. 175° (Found : C, 53·7; H, 4·6; Cl, 21·7. Calc. for $C_7H_7O_2Cl$: C, 53·0; H, 4·5; Cl, 22·4%).

A suspension of the chlorotoluquinol (3·6 g.) in acetic anhydride (5·1 g.) and acetic acid (5·4 g.) was treated with 72% perchloric acid (1 drop); the temperature rose rapidly to 55° and complete dissolution occurred. After *ca.* 1 minute the mixture was decomposed with ice, and the resulting solid crystallised first from alcohol and then from benzene–light petroleum. *4-Chlorotolu-2 : 5-quinol diacetate* (2 : 5-*diacetoxy-4-chlorotoluene*) separated in colourless needles, m. p. 112—113° (Found : C, 54·3; H, 4·6; Cl, 14·9. $C_{11}H_{11}O_4Cl$ requires C, 54·4; H, 4·5; Cl, 14·6%).

Evaporation of the original chloroform solution after filtration of (*A*) gave a brown solid (2 g.), m. p. 105—107°, which crystallised from benzene in light brown needles, m. p. 113—116°. With acetic anhydride–acetic acid (1 : 1) and a trace of 72% perchloric acid this gave (?) 2 : 5-*diacetoxy-3 : 4-dichlorotoluene*, colourless needles (from methanol), m. p. 124° (Found : C, 47·6; H, 3·8; Cl, 25·6. $C_{11}H_{10}O_4Cl_2$ requires C, 47·7; H, 3·6; Cl, 25·6%).

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138. *Anionic Polymerisation. Part I. The Polymerisation of Styrene in Liquid Ammonia Solution catalysed by Potassium Amide.*

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In an earlier paper (Evans, Higginson, and Wooding, *Rec. Trav. chim.*, 1949, **68**, 1069) a mechanism was suggested for the polymerisation of styrene in liquid ammonia as solvent, catalysed by potassium amide. The study, there reported, of the dependence of molecular weight on reactant concentrations has been extended and measurements of the rate of styrene disappearance have been made. These results confirm the mechanism previously suggested which involves: initiation by addition of the amide ion to a styrene molecule, propagation by reaction of the resulting carbanion with further monomer molecules, and termination by reaction of the growing polymer chain with the solvent ammonia leading to re-formation of the amide ion.

The activation energy and frequency factor of the initiation reaction have been found.

In contrast to the many detailed investigations of the polymerisation of vinyl monomers by radical and cationic initiators, the studies of polymerisation by anionic catalysts have been almost entirely qualitative in character. Such anionic polymerisation is known to occur in the bulk monomer, and in solution in inert hydrocarbons, diethyl ether, and liquid ammonia, the catalysts including alkali metals (Beaman, *J. Amer. Chem. Soc.*, 1948, **70**, 3115; Schlenk and Bergmann, *Annalen*, 1928, **463**, 1; Ziegler *et al.*, *ibid.*, 1934, **511**, 13, 64), sodium amide (Sanderson and Hauser, *J. Amer. Chem. Soc.*, 1949, **71**, 1595), triphenylmethylsodium (Beaman, *loc. cit.*), metal alkyls (Ziegler *et al.*, *Annalen*, 1934, **511**, 13, 45; 1940, **542**, 90), and Grignard reagents (Landler, *Rec. Trav. chim.*, 1949, **68**, 922). In aqueous solution the polymerisation of nitro-olefins (Blomquist, Tapp, and Johnson, *J. Amer. Chem. Soc.*, 1945, **67**, 1519) probably involves an anionic mechanism also, but for most vinyl monomers the strongest base obtainable in water, the hydroxyl ion, is unreactive.

Of the various reaction systems which could be investigated in detail, homogeneous polymerisation in liquid ammonia as solvent with the amide (NH_2^-) ion as catalyst seemed likely to present least interpretative difficulties. In particular, information is available as to the state of dissolved salts in this solvent. From the findings reported in a preliminary communication (Evans, Higginson, and Wooding, *loc. cit.*) it was evident that styrene, methyl methacrylate, and acrylonitrile undergo polymerisation under conditions suitable for kinetic measurements, and the following mechanism for the reaction was proposed:

$$NH_2^- + CH_2{:}CHR \longrightarrow NH_2{\cdot}CH_2{\cdot}\overset{(-)}{C}HR \quad (\textit{Initiation})$$

$$NH_2{\cdot}[CH_2{\cdot}CHR]_m{\cdot}CH_2{\cdot}\overset{(-)}{C}HR + CH_2{:}CHR \longrightarrow NH_2{\cdot}[CH_2{\cdot}CHR]_{m+1}{\cdot}CH_2{\cdot}\overset{(-)}{C}HR \quad (\textit{Propagation})$$

$$NH_2{\cdot}[CH_2{\cdot}CHR]_n{\cdot}CH_2{\cdot}\overset{(-)}{C}HR + NH_3 \longrightarrow NH_2{\cdot}[CH_2{\cdot}CHR]_n{\cdot}CH_2{\cdot}CH_2R + NH_2^- \quad (\textit{Termination})$$

Sanderson and Hauser (*loc. cit.*) have suggested a similar reaction mechanism.

The main purpose of the work here described has been the verification of the above reaction scheme in one specific case. Styrene was selected as a suitable monomer since here side reactions proved to be unimportant.

Experimental

1. *Materials.—Styrene.* The commercial product was washed twice with 10% sodium hydroxide solution, then six times with distilled water. After drying ($CaCl_2$), the monomer was distilled under water-pump vacuum in a stream of dry, oxygen-free nitrogen, at about 30°. The purified styrene, which was prepared in small quantities as required, was tested for polymer

by dilution in excess of pure methanol before use; small amounts of polymer cause a turbidity in the solution.

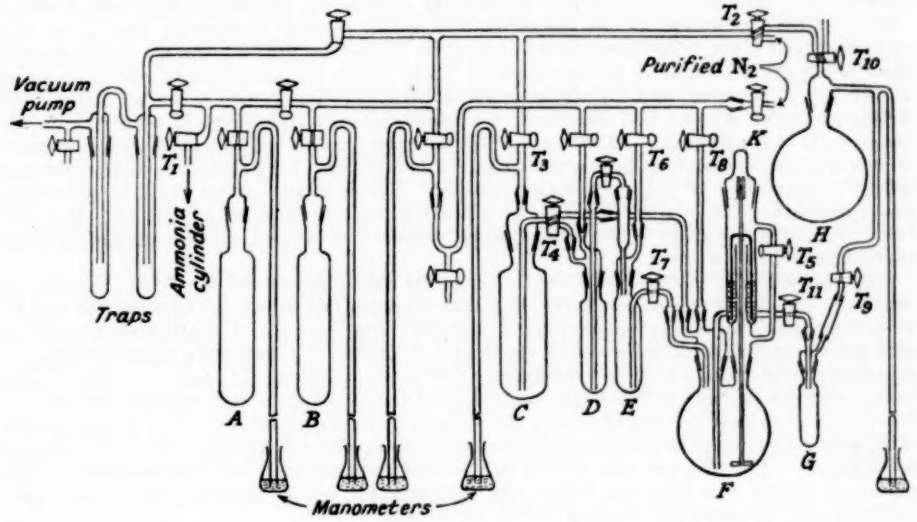
Toluene and light petroleum (b. p. 40—60°) were purified by distillation and stored over metallic potassium.

For freezing-point determinations, spectroscopic *cyclo*hexane (m. p. 2·4°) was purified by fractional crystallisation, and was then fractionally distilled over sodium through a 14" glass column, the 80·5—80·8° fraction being retained (m. p. 4·8°; lit., 6·5°).

Benzene for viscosity determinations was either " molecular weight benzene, cryoscopically pure " or " AnalaR " grade.

Iodine monochloride reagent was prepared in 0·1M-solution by dissolving the appropriate amount of pure iodine monochloride in glacial acetic acid. Alternatively, chlorine was passed slowly into a cooled 0·1N-solution of iodine in glacial acetic acid, until the titration against sodium thiosulphate solution was almost doubled. A slight excess of iodine remained, but was preferable to an excess of chlorine, for in the latter case irreproducible results were obtained in

FIG. 1.



the determination of styrene. The reagent was kept in absence of light and was stable for a month.

Other reagents used were either obtained pure, or were purified by the usual methods.

Nitrogen from a cylinder was purified by slow passage through a trap surrounded by liquid air, which removed most of the moisture present, and then through three traps in series containing a concentrated solution of potassium in liquid ammonia, cooled to −78°. These traps removed any remaining moisture and also oxygen. A 2-l. bulb and mercury blow-off prevented sudden pressure fluctuations during withdrawal of pure nitrogen.

2. *Liquid Ammonia Apparatus.*—The apparatus for manipulation of liquid ammonia solutions in absence of air follows accepted practice (see, *e.g.*, Kraus and Hawes, *J. Amer. Chem. Soc.*, **1933**, **55**, 2776; Laitinen and Nyman, *ibid.*, 1948, **70**, 2241; Zintl, Goubeau, and Dullenkopf, *Z. physikal. Chem.*, **1931**, *A*, **154**, 1) and is shown in Fig. 1. Those parts of the apparatus through which ammonia was passed as liquid were detachable for cleaning. Taps and joints were greased with silicone tap grease.

(a) *Purification of ammonia.* Cylinder ammonia, led in as gas through tap T_1, was condensed on to sodium in vessel *A*, which was cooled to −78° (approx.) by acetone–solid carbon dioxide. By warming *A* and cooling *B* ammonia was then distilled into vessel *B*, which also contained metallic sodium. The ammonia was then distilled into the storage vessel *C*. Two such distillations from sodium were found adequate to free the ammonia from water and oxygen, both of which can react with potassium amide or with carbanions in liquid ammonia. From *C*

the ammonia can be either distilled into vessels *D*, *E*, or *F*, or forced directly into *D* or *F* by application of a pressure of pure nitrogen through taps T_2 and T_3 to vessel *C*, the receiving vessel being cooled.

(b) *Preparation of the potassium amide solutions.* An appropriate quantity of pure potassium (0·1—5·0 g.), cut free from contaminated surfaces, was weighed under toluene and transferred to flask *E* under light petroleum (b. p. 40—60°). A small amount of baked platinised asbestos (5% Pt, as supplied by B.D.H. Ltd.) wrapped in platinum gauze was added as catalyst for amide formation.

The light petroleum was pumped off, and ammonia distilled from *C* up to a previously determined mark in *E*. In absence of moisture and oxygen, potassium amide formed slowly during several hours at −33·5°, and at complete conversion a clear, pale yellow solution remained. The presence of moisture or oxygen resulted in a cloudy solution due to the formation of insoluble potassium hydroxide or potassium peroxide and the rate of disappearance of the blue colour of the potassium solution was comparatively rapid. Potassium amide solutions thus contaminated were rejected.

(c) *Preparation of solutions of styrene in liquid ammonia.* Solutions of styrene were prepared in *F* by pipetting in the appropriate quantity of purified styrene, which was then frozen at −78°. After evacuation, liquid ammonia was passed in from *C* through tap T_4 up to a predetermined mark. The temperature was then altered to −33·5°, the ammonia pressure then being equal to that of the atmosphere. Tap T_5 on the mercury-seal stirrer was now closed, cap *K* removed, and the stirrer operated by connecting it with a flexible metal drive. When the solid styrene had dissolved, the temperature was lowered if necessary to the appropriate value (between −33·5° and −64°), and the pressure kept at 1 atm. with nitrogen. A Dewar vessel surrounding the reaction vessel *F* was fitted with a copper circulating coil through which acetone at −78° was continually pumped. Thermostatic control could be effected at any temperature from −70·0° upwards by a heating coil controlled by a " Sunvic " type TS3 bimetallic strip regulator. The temperature variation measured on a standard pentane thermometer was ±0·5°.

(d) *Production of polymer samples for molecular-weight determination.* With the styrene dissolved, the stirrer was disconnected, and after nitrogen had blown out through the seal for several minutes, cap *K* was replaced and T_5 opened. Application of a small excess pressure of nitrogen through T_6 with, if necessary, slight suction applied to *F* enabled a suitable amount of potassium amide solution to be transferred from vessel *E* through T_7 into *F*. Tap T_7 was closed, and the pressure in *F* brought up to that of the atmosphere with nitrogen through T_8. The stirrer was connected as before, and the mixture continually stirred. After an appropriate time, solid ammonium chloride was added through a stoppered side tube (not shown in diagram) to vessel *F*. The mixture was stirred for several minutes to allow neutralisation of the potassium amide, and then the stirrer was disconnected, cap *K* replaced, the Dewar vessel removed, and the ammonia distilled back to vessel *A*.

(e) *Kinetic experiments.* The potassium amide solution was added to the styrene solution as described above. At the same time a stop-watch was started. Vessel *G* contained 1 g. of solid ammonium nitrate and was immersed in acetone–solid carbon dioxide (−78°) and evacuated through T_9 and T_{10}. After a suitable time T_{10} was closed and T_{11} opened. In ten seconds about 20—40 ml. of the reaction mixture passed over into *G*, and the ammonium nitrate immediately stopped the reaction by neutralising the potassium amide. The pressure in *F* remained constant as nitrogen at 1 atm. pressure had access to this vessel through T_8. No liquid remained in the tube connecting *F* and *G* after sampling, for on closure of T_{11} the ammonia near this tap boiled and blew the solution back into *F* and *G* respectively. After sampling, the cooling bath was removed from *G*, and the pressure brought up to that of the atmosphere through T_{10}; *G* was then removed and replaced by a similar vessel, also containing 1 g. of ammonium nitrate, which was evacuated ready for taking the next sample. The amount of the reaction sample was determined to ±2% by measuring the height of the liquid in the calibrated vessel *G*. The contents of *G* were transferred to a cooled, 500-ml., conical flask and *G* was then washed three times with pure chloroform, the washings being added to the bulk liquid in the conical flask. Ammonia was allowed to boil off in a fume cupboard, and the sample analysed for styrene as described below. With this procedure samples could be taken every two minutes if required. The volume of reaction mixture before sampling was 400—500 ml. and up to 15 samples were taken in each kinetic experiment. Values for the initial styrene concentration could be obtained by taking a sample before adding the potassium amide solution: the above procedure was used except that ammonium nitrate in *G* was not necessary.

The values thus found agreed well with those obtained from the volumes of styrene and liquid ammonia used.

3. *Molecular-weight Determinations.*—(a) *Purification of polymer.* After polymerisation, the ammonia was distilled off and the polystyrene and unchanged styrene remaining in vessel *F* were dissolved in a total of 60 ml. of ethyl methyl ketone. The solution was stirred mechanically, and *F* was washed with 60 ml. of water, the washings being added to the ethyl methyl ketone solution; 400 ml. of methanol were then added slowly, and stirring was continued for two hours. The precipitated polymer was collected on a sintered filter, washed with water and methanol, and then redissolved through the filter with 60 ml. of ethyl methyl ketone. This solution was mechanically stirred, and 600 ml. of methanol followed by 100 ml. of water were added slowly. After 2 hours' stirring, 5 g. of potassium chloride were added, and stirring was continued for a further 2 hours. The polymer was then filtered off, washed thoroughly with water and with methanol, and then dried (P_2O_5) in high vacuum for 48 hours.

(b) *Viscosity determinations.* Viscosity determinations were made at 25° in benzene as solvent, an Ostwald viscometer, B.S.S. type, No. 1, being used. Solutions of polymer were prepared by weighing the requisite amount, less than 1 g. per 100 ml. of benzene, into a standard flask. The solutions were kept at 25° before being made up to the mark, and before use, 10 ml. of solution were pipetted into the viscometer, which was held vertically in a clamp fitted with a spirit-level and adjusting screws. The time of flow was taken with a $\frac{1}{5}$-second stop-watch. The average of five determinations with a given solution was taken, and two separate solutions were made up for each concentration of a particular polymer sample. The time of flow of the pure benzene was also determined.

(c) *Nitrogen determinations.* Nitrogen in the polymer was determined by the standard Kjeldahl method. A mixed catalyst of 0·25 g. of metallic selenium with 0·25 g. of copper sulphate was used in the conversion of nitrogen in the polymer into ammonium sulphate by ashing with concentrated sulphuric acid. The amount of polymer used was not less than 0·4 g. The ammonia was distilled into a known excess of 0·01N-sulphuric acid, and the solution back-titrated with 0·01N-sodium hydroxide solution, bromocresol-green being used as indicator.

(d) *Freezing-point determinations.* The freezing-point apparatus consisted of a 3-cm. diameter tube fitted with a stirrer and Beckmann thermometer, and was held by a cork ring in an 8-cm. diameter tube. The latter was immersed in an ice–water mixture which was mechanically stirred. The freezing point was determined from the cooling curves, the rate of cooling at 3·5° being approximately 0·05° per min. The molecular depression constant for 100 g. of the solvent used, *cyclo*hexane (m. p. 4·8°), was determined as 204·7 (±1·0) by using pure naphthalene [compare the value of 201·5 for pure *cyclo*hexane (m. p. 6·5°)]. Polymer solutions were examined at several concentrations, from 0·8 to 3·4 g. of polymer per 100 g. solvent.

4. *Determination of Unchanged Styrene in the Presence of Polymer.*—The usual bromine method for the determination of styrene (Ulrig and Levin, *Ind. Eng. Chem. Anal.*, 1941, **13**, 90) was inapplicable to the polystyrene–styrene mixtures obtained during kinetic experiments, high and irreproducible values being obtained. Experiments showed that 2-phenylethylamine, the simplest compound obtained by the attack of potassium amide on styrene in liquid ammonia, reacted slowly with bromine under the conditions of the estimation. However, the iodine chloride method of determining vinyl groups (see, *e.g.*, Jeu and Alyea, *J. Amer. Chem. Soc.*, 1933, **55**, 575) was found to give exact and reproducible results for styrene even in the presence of similar amounts of 2-phenylethylamine and of a large excess of ammonium acetate. On the other hand, the polymer, freed from styrene and the lower molecular weight polystyrenes (up to about tetramer) by the precipitation procedure described above, showed no sign of unsaturation even when bromine in chloroform–acetic acid was used as solvent. The average molecular weight was sufficiently low to enable one ethylenic link per polymer chain to be detected.

The procedure adopted for determining unchanged styrene in the kinetic experiments was as follows. A conical flask containing the sample, dissolved in chloroform and saturated with ammonia, was cooled to −50°, and glacial acetic acid added slowly with continuous shaking till present in excess. After this had attained room temperature, an approximately 50% excess of 0·1M-iodine monochloride reagent was added, and the stoppered flask kept for 15 minutes with occasional shaking. Low results were obtained if the time of standing was less than 10 minutes; 10—30 minutes' standing gave reproducible results. At the end of the 15 minutes a small excess of 10% aqueous potassium iodide solution was added, and liberated iodine titrated against 0·1N-sodium thiosulphate solution. For each set of samples analysed, blank titrations

were done in duplicate to standardise the iodine chloride solution, the same conditions being used except for the absence of reaction mixture.

It was thus possible to determine styrene in amounts of 0·1 g. and over with an accuracy of ±3%. The most dilute samples determined were approximately 0·01M in styrene, and as for these samples 40 ml. of the reaction mixture were taken, the amount of styrene determined was about 0·04 g.; here the error was ±10%, *i.e.*, ±0·004 g. of styrene, approximately the same as the error found in determining larger quantities of styrene.

5. *Conductivity Measurements.*—A 500-ml. flask fitted with platinum electrodes of approximately 1 sq. cm. area and 0·5 cm. apart was used as a conductivity cell and was attached to the liquid-ammonia apparatus in the same manner as vessel *F*. The electrodes were platinised according to Popoff, Kunz, and Snow's procedure (*J. Physical Chem.*, 1928, **32**, 1056). After being washed with water they were dried by washing with ethanol and then with dry ether.

Potassium amide solutions were prepared in the conductivity vessel by using known amounts of metallic potassium and liquid ammonia. The platinised electrodes served as catalyst for the conversion of the potassium solution into potassium amide. Measurements were made in the low-temperature thermostat described above.

The resistance of the solution was determined by using an A.C. bridge fitted with a variable condenser for balancing stray capacitance. The oscillator provided 5 v at 1000 cycles per second. The detector circuit consisted of an amplifier giving a D.C. output fed to a "magic eye" indicator for rough balancing and to a D.C. galvanometer for more precise adjustment.

Results

1. *Molecular Weights.*—(a) *Molecular weights by viscosity measurements.* The intrinsic viscosity, $[\eta]$, can be found by extrapolation of plots of either $(\eta \text{ spec.})_c/c$ against c or $\ln (\eta \text{ rel.})_c/c$ against c to infinite dilution. Here $(\eta \text{ spec.})_c$, the specific viscosity at concentration c, is $[(\eta \text{ solution})_c - (\eta \text{ solvent})]/(\eta \text{ solvent})$, and $(\eta \text{ rel.})_c$, the relative viscosity at concentration c, is $(\eta \text{ solution})_c/(\eta \text{ solvent})$. As $(\eta \text{ spec.})_c/c$ increases with increase in c while $\ln (\eta \text{ rel.})_c/c$ decreases with c, $[\eta]$ can be found if c is small by taking the arithmetic means of $(\eta \text{ spec.})_c/c$ and $\ln (\eta \text{ rel.})_c/c$ (cf. Baxendale, Bywater, and Evans, *J. Polymer Sci.*, 1946, **1**, 241). This procedure was used here. In a few cases values of $[\eta]$ were found from measurements at more than one concentration between 0·2 and 0·8 g. of polymer per 100 ml. of solution in benzene. The largest difference found between any two values of the intrinsic viscosity for a given polymer sample was less than 10%, and in one or two cases differences of this magnitude were found between intrinsic viscosities obtained from solutions of similar concentrations.

In Table 1 are tabulated the intrinsic viscosity $[\eta]$ and the corresponding weight-average molecular weight W calculated by using the Staudinger equation constant of Kemp and Peters (*Ind. Eng. Chem.*, 1942, **34**, 1097) for low molecular weight polystyrenes. For the concentration units used here (c = g. of polymer per 100 ml. of solution in benzene), $K = 3{\cdot}6 \times 10^{-5}$. In addition, molecular-weight values obtained by using Bamford and Dewar's constants (*Proc.*

Table 1. *Molecular weights from viscosity, nitrogen content, and freezing-point depression measurements.*

Sample from expt.	$[\eta]$	Viscosity mol. wts. ($\overline{W}$) *: K. & P.	B. & D.	Number average mol. wts. ($\overline{N}$): N content	F.-p. depn.	Sample from expt.	$[\eta]$	Viscosity mol. wts. ($\overline{W}$.) *: K. & P.	B. & D.	Number average mol. wts. ($\overline{N}$): N content	F.-p. depn.
MW	0·0418	1160	1110	—	—	MH	0·0806	2240	3040	2180, 2800	2200
MA	0·0515	1430	1520	—	—	MG	0·0825	2290	3150	1980, 2180	2625
MX	0·0540	1500	1640	1410	—	MN	0·0856	2380	3360	2400, 2450	—
MB	0·0558	1550	1720	—	—	MQ	0·0882	2450	3480	—	—
NA	0·0591	1640	1880	—	2050	MD	0·0887	2460	3510	—	—
MR	0·0595	1650	1890	—	—	MF	0·0907	2520	3640	—	—
NB	0·0649	1800	2170	2630, 2700	<3000	ML	0·0962	2670	4000	—	—
MC	0·0703	1950	2450	—	—	MP	0·1016	2820	4330	—	—
ME	0·0735	2040	2630	2270, 2880	—	ND	0·1180	3280	5480	3700	—
MT	0·0739	2050	2650	—	—	MU	0·1184	3290	5500	—	—
MS	0·0752	2090	2730	—	—	MJ	0·1230	3410	5820	3320	—
NC	0·0768	2130	2820	2880, 3190	2760	MK	0·1310	3640	6410	3020, 3400	—
MM	0·0774	2150	2840	—	—	MV	0·1531	4250	8150	—	—

* K. & P. = Kemp and Peters (*loc. cit.*); B. & D. = Bamford and Dewar (*loc. cit.*).

Roy. Soc., 1948, *A*, **192**, 329) are tabulated. These authors use Mark and Houwink's modification of the original Staudinger equation and find $K = 4{\cdot}39 \times 10^{-4}$, c being expressed in the same units as above and β, the molecular-weight exponent, being taken as 0·65; these values appear to be applicable to low molecular weight polystyrenes.

(b) *Molecular weights by nitrogen determination.* The molecular weights found by nitrogen determination in the polymer are also recorded in Table 1. They have been calculated by assuming one nitrogen atom per polymer molecule.

(c) *Molecular weights by freezing-point depression.* The molecular weight of 2-phenylethylamine as calculated from the depression of freezing point of *cyclo*hexane was found to increase with concentration. Linear extrapolation to zero concentration led to a value of 119·8 (Calc. : 121·2). A few polymer molecular weights were determined in this way and are recorded in Table 1. Two freezing-point depression measurements at each of several different concentrations were made and extrapolated to zero concentration. The concentrations varied between 0·7 and 3·4 g. of polymer per 100 g. of *cyclo*hexane. The method was limited to polymer samples of molecular weight below about 3000. Above this figure the polymer was found to be incompletely soluble in *cyclo*hexane.

Although the accuracy of the molecular weights by freezing-point depression and by nitrogen content determination is not high, comparison shows a fair agreement, much better than that obtained by assuming two nitrogen atoms per polymer molecule in calculating the molecular weight from nitrogen content, which would give double the molecular weights tabulated. This correlation between the two sets of figures, both number-average molecular weights, may be taken as evidence for one nitrogen atom per polymer chain. The two sets of viscosity molecular weights, derived from the same values of $[\eta]$, but using different intrinsic viscosity–molecular weight relationships may now be compared with the molecular weights by nitrogen content. In general, the weight-average and the number-average molecular weights of an unfractionated polymer sample are not identical. For these polymers, however, up to a molecular weight of about 2500—3000 both sets of viscosity (weight-average) molecular weights are in reasonable agreement with the nitrogen content (number-average) molecular weights. Above this value, although fair agreement between the molecular weights found by using Kemp and Peters's constants and the molecular weights found by nitrogen content determination is still apparent, yet the corresponding values found by using Bamford and Dewar's constants are very much larger. The values based on the work of Kemp and Peters have therefore been chosen, as it seems probable that the agreement between number-average and weight-average molecular weights found at the lower molecular weights would still be found at the higher molecular weights.

Conductivity Measurements : Variation of the Dissociation Constant of Potassium Amide with Temperature.—Although $K_{diss.}$ for potassium amide in liquid ammonia has been accurately measured at −33·5° (Hawes, *J. Amer. Chem. Soc.*, 1933, **55**, 4422), no measurements have been made at lower temperatures. The purpose of the conductivity measurements was to determine the approximate magnitude of the variation with temperature.

In the calculation of the dissociation constant of potassium amide from conductivity measurements, extrapolation of the equivalent conductivity to infinite dilution is valueless unless measurements of high accuracy at concentrations lower than 10^{-3}M have been made (see Fuoss and Kraus, *ibid.*, p. 487). On the other hand, 10^{-3}M-potassium amide is the lowest concentration for which reasonably accurate measurements can be made without recourse to laborious high-precision work of the type described by Hnizda and Kraus (*ibid.*, 1949, **71**, 1565). However, we may in general assume that the equivalent conductivity at infinite dilution of a given solute at a particular temperature is inversely proportional to the viscosity of the solvent at the same temperature (Walden, *Z. physikal. Chem.*, 1912, **78**, 257). Thus, provided that Λ_0 is known at a given temperature and the temperature dependence of the solvent viscosity is known, Λ_0 can be calculated for any temperature.

Hawes (*loc. cit.*) has found the value 343 mhos for $(\Lambda_0)_{KNH_2}$ at −33·5°, and Fredenhagen (*Z. anorg. Chem.*, 1930, **186**, 13) and Monosson and Pleskov (*Z. physikal. Chem.*, 1931, *A*, **156**, 192) have determined the viscosity of liquid ammonia at various temperatures from −33·5° to −69°. Hence, for an approximate measure of the temperature variation of $K_{diss.}$ it is necessary only to take conductivity measurements at a potassium amide concentration of about 10^{-2}M, where reasonable accuracy is possible and no extrapolation to infinite dilution is needed. Since only approximate $K_{diss.}$ values are required, the Ostwald dilution law may be used provided the concentration of potassium amide is not too high.

The conductivity of solutions of potassium amide in liquid ammonia was determined at

$-33{\cdot}5°$, $-45°$, $-60°$, and $-70°$ at six different concentrations between $1{\cdot}7 \times 10^{-3}$ and $2{\cdot}79 \times 10^{-2}$M. Measurements were made at each of the four temperatures, the same solutions being used. Over this range of concentrations a plot of $(\Lambda_c)_T$ against $(\sqrt{c})_T$ is approximately linear (cf. Fuoss and Kraus, *loc. cit.*), though, as mentioned previously, the extrapolation of such a plot to zero concentration yields an incorrect value for $(\Lambda_0)_T$. From these linear plots the value of $(\Lambda)_T$ at a concentration of 10^{-2}M-potassium amide was taken, and with the appropriate values of $(\Lambda_0)_T$ the use of the Ostwald dilution law enables $(K_{\text{diss.}})_T$ to be calculated (Table 2).

TABLE 2.

Temp.	$-33{\cdot}5°$	$-45°$	$-60°$	$-70°$
$(\eta)_T$, centipoise	0·260	0·304	0·383	0·486
$(\Lambda_0)_T$, mhos	343	287	228	191
$(\Lambda_{c=0{\cdot}01})_T$, mhos	33·0	31·0	26·0	22·5
10^4 $(K_{\text{diss.}})_T$	1·02	1·31	1·47	1·57

A value of $c = 0{\cdot}01$ was taken as being the lowest possible consistent with reasonable accuracy in c. Higher values of c were not used in the calculation since, the Ostwald dilution law being used, the effect of ionic strength on ionic mobility would lead to greater inaccuracy in $K_{\text{diss.}}$.

We see from Table 2 that $K_{\text{diss.}}$ varies little with temperature from $-33{\cdot}5°$ to $-70°$. This small temperature dependence of $K_{\text{diss.}}$ is probably not significant in view of the approximate nature of these results and we conclude that $(\Delta H)_{\text{diss.}} = 0 \pm 2$ kcal./mole. The value of $1{\cdot}02 \times 10^{-4}$ for $K_{\text{diss.}}$ at $-33{\cdot}5°$ compares with $7{\cdot}0 \times 10^{-5}$ (Franklin, *Z. physikal. Chem.*, 1909, **69**, 290) and $7{\cdot}3 \times 10^{-5}$ (Hawes, *loc. cit.*). The latter value is probably the most accurate recorded and is used throughout this work over the temperature range $-33{\cdot}5°$ to $-70°$.

General.—(a) *Molecular weights.* (i) Dependence of weight-average molecular weight on the concentrations of potassium amide, amide ion, and potassium ion. The figures in Table 3 show

TABLE 3.

Temperature = $-33{\cdot}5°$.

Expt.	Viscosity mol. wt.	$[C_8H_8]$,* mole/l. $\times 10^2$	$[KNH_2]$, mole/l. $\times 10^2$	[KI], mole/l. $\times 10^2$	$[K^+]$, mole/l. $\times 10^3$	$[NH_2^-]$, mole/l. $\times 10^3$	Formation of visible polymer
MW	1160	9·0	1·54	5·50 †	13·06	0·086	Slow
MX	1500	11·3	1·64	1·96 †	7·13	0·168	Slow
MC	1950	9·7	1·34	—	0·99	0·99	Immediate
MB	1550	9·5	4·96	—	1·90	1·90	Immediate
MA	1430	8·45	6·48	—	2·17	2·17	Immediate

* In this and later tables, C_8H_8 is used for styrene.

† The potassium-ion concentration in MW and MX was calculated by using the value of $4{\cdot}067 \times 10^{-3}$ for the dissociation constant of potassium iodide at $-34°$ (Hnizda and Kraus, *loc. cit.*).

that the molecular weight is relatively unaffected by the concentration of the amide ion or of undissociated potassium amide, the deviations being apparently random. Experiments MW, MX, and MC also show that the presence of different amounts of potassium ion has no marked effect on the molecular weight.

(ii) Dependence of weight-average molecular weight on concentration of styrene. In Table 4 are shown the results of experiments in which the concentration of potassium amide was kept roughly constant, while that of styrene was varied. It can be seen (Fig. 2) that the molecular weight shows an approximately linear dependence on the initial styrene concentration up to about 0·3M-styrene. At concentrations greater than this, the linear relationship breaks down and the molecular weights are very much lower than would be expected.

It will be noted that the percentage yield of polymer increases with the initial concentration of styrene. This is to some extent due to the higher proportion of low molecular weight polymer separated with unchanged styrene after reaction in the experiments at lower initial styrene concentrations. The rate of polymerisation is lower in the low styrene concentration experiments, but this was partly offset by increasing the time of polymerisation from 25 minutes for the more concentrated solutions to 60 minutes for the more dilute. A constant percentage conversion of styrene was not attained in these experiments, as this requires a knowledge of the rate of disappearance of styrene and the corresponding kinetic experiments were done subsequently.

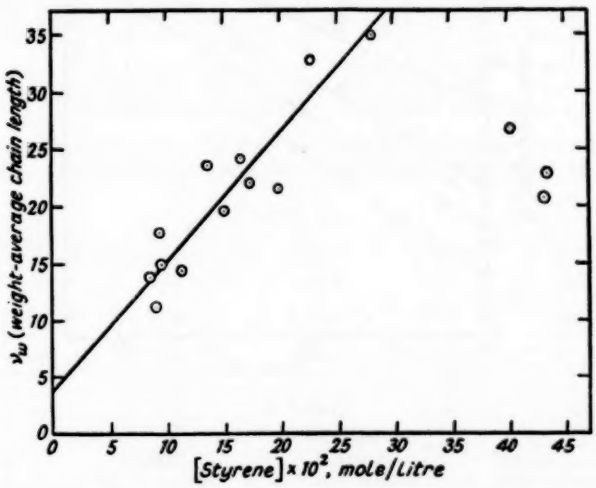
TABLE 4.

Temperature = − 33·5°.

Expt.	$[C_8H_8]$, mole/l. × 10^2	$[NH_2^-]$, mole/l. × 10^3	Approx. yield, % *	W	ν_w †	$\overline{W}$ (B. & D.)
MA	8·45	2·13	26·5	1430	13·75	1520
MW	9·0	0·09	—	1160	11·1	1110
MB	9·5	1·86	38·5	1550	14·9	1720
MC	9·7	0·97	35·0	1950	18·75	2450
MX	11·3	0·17	—	1500	14·4	1640
MD	13·5	0·94	50·0	2460	23·65	3510
ME	15·0	0·86	66·5	2040	19·6	2630
MF	16·55	1·28	43·5	2520	24·2	3640
MG	17·3	0·92	68·0	2290	22·0	3150
MH	19·8	0·97	76·0	2240	21·55	3040
MJ	22·7	0·86	62·0	3410	32·8	5820
MK	28·2	0·65	76·5	3640	35·0	6410
ML	40·2	0·93	83·0	2670	25·67	4000
MM	43·2	0·77	—	2150	20·67	2840
MN	43·5	0·97	82·0	2380	22·9	3360
MP	62·5	0·88	81·0	2820	27·1	4330
MQ	65·1	0·97	86·0	2450	23·55	3480

* Measured on polymer separated by precipitation procedure.
† Weight-average chain length.

FIG. 2.



Under otherwise equivalent conditions there appeared to be a small decrease in the molecular weight of the polymer as the time of reaction was increased, *i.e.*, the molecular weight decreased slightly with increased yield of polymer. This effect was barely greater than the overall experimental error of the polymerisation experiments. Sanderson and Hauser (*loc. cit.*) have observed similar behaviour in the styrene–sodium amide–liquid ammonia system.

(iii) Dependence of the weight-average molecular weight on temperature. In the case of the molecular weights determined at temperatures lower than −33·5°, recorded in Table 5, the corresponding kinetic measurements had been made previously and it was therefore possible by adjusting the time of reaction to ensure 50% reaction in each case, with a corresponding yield of polymer of rather less than this figure. These results show that the molecular weight increases with decrease in temperature, a drop of 25° causing a 2—3-fold increase in W.

(b) *Kinetic results.* (i) Dependence of rate of disappearance of styrene on styrene concentration. In Table 6 are summarised the results of six kinetic experiments at −33·5° in which the concentration of potassium amide was kept constant and the initial styrene concentration was varied. It was found that the rate of disappearance of styrene was of second order with respect to the styrene concentration, as good linear plots of $1/[\text{Styrene}]_t$

against t were obtained (Fig. 3). Other kinetic expressions led to curved plots of the appropriate function of the styrene concentration against time.

TABLE 5.*

I	II	III	IV	V	VI	VII	VIII	IX	X	XI	XII
From gradient of Fig. 2		−33·5°	—	—	—	—	5·28	—	3·7226	—	4·171
MR	½	−33·5	10·2	1·01	1650	15·85	5·58	4·28	3·7463	3·6316	4·171
MS	¾	−36·0	12·5	1·13	2090	20·05	6·16	4·63	3·7898	3·6653	4·215
MT	3	−44·0	8·6	0·91	2050	19·7	8·76	6·59	3·9426	3·8186	4·363
MU	6	−54·0	10·0	0·93	3290	31·6	13·24	9·60	4·1221	3·9823	4·562
MV	9½	−59·0	10·9	1·00	4250	40·8	16·20	11·52	4·2096	4·0614	4·669

* *Key* : Col. I, Expt.
,, II, Time of reaction (hrs.) for 50% conversion.
,, III, Temperature (°c.).
,, IV, Initial styrene concn., moles/l. × 10^2.
,, V, [KNH_2], moles/l. × 10^3.
Col. VI, $\overline{W}$.
,, VII, Average chain length, ν_w.
,, VIII, $k_p/k_t \times 10^{-3}$ (equation 11).
,, IX, $k_p/k_t \times 10^{-3}$ (,, 10).
,, X, log k_p/k_t (,, 11).
,, XI, log k_p/k_t (,, 10).
,, XII, $10^3/T$.

FIG. 3.

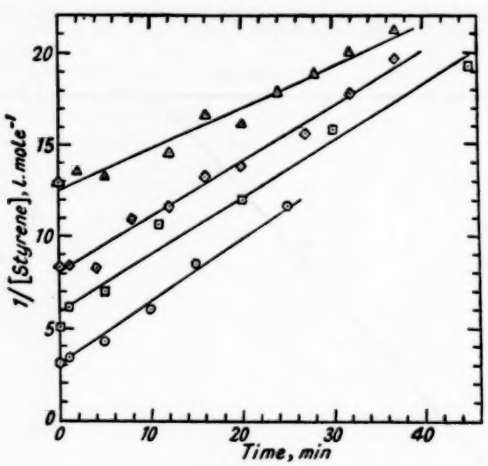


TABLE 6.

Temperature = − 33·5°.

Expt.	Initial [C_8H_8], mole/l. × 10^2	[KNH_2], mole/l. × 10^2	[NH_2^-], mole/l. × 10^3	d(1/[C_8H_8])/dt, l. mole^{-1} min.$^{-1}$
KA	5·75	1·15	0·88	0·357
KB	11·90	1·25	0·92	0·300
KC	14·35	1·00	0·82	0·233
KD	19·70	1·02	0·83	0·317
KE	21·80	1·07	0·85	0·248
KF	32·40	1·23	0·91	0·328

TABLE 7.

Temperature = − 33·5°.

Expt.	Initial [C_8H_8], mole/l. × 10^2	[KNH_2], mole/l. × 10^2	[NH_2^-], mole/l. × 10^3	Slope = d(1/[C_8H_8])/dt, l. mole^{-1} min.$^{-1}$	k' = Slope / [KNH_2]$^{\frac{1}{2}}$	k'' = Slope / [NH_2^-]
KG	9·80	0·36	0·48	0·100	1·67	208
Average of KA to KF	5·75—32·4	1·12 (av.)	0·87 (av.)	0·297	2·81	342
KB	11·90	1·25	0·92	0·301	2·69	326
KH	9·60	9·4	2·58	1·185	3·86	458
KJ	9·23	15·1	3·29	1·420	3·65	431
KK	9·90	22·3	4·00	1·815	3·84	453

(ii) Dependence of rate on potassium amide and amide ion concentrations. To determine the dependence of the rate on potassium amide concentration, experiments were done in which the concentration of potassium amide was varied from $3{\cdot}6 \times 10^{-3}$ to 0·223M. These are recorded in Table 7. Plots of the slopes of these reaction plots against the square root of the potassium amide concentration and against the amide-ion concentration are shown in Figs. 4*a* and 4*b*. Fairly good straight lines are obtained. The overall kinetic expression can thus be written as

$$d[\text{Styrene}]/dt = -k'[\text{Styrene}]^2[KNH_2]^{\frac{1}{2}}$$

or

$$d[\text{Styrene}]/dt = -k''[\text{Styrene}]^2[NH_2^-]$$

Since under the experimental conditions $[NH_2^-]^2 \simeq K_{\text{diss.}} \times [KNH_2]$, it is not possible to differentiate between these two expressions on experimental grounds and they do not necessarily imply the same detailed kinetic mechanism. Reasons for preferring the second expression will be given later.

FIG. 4*a*.

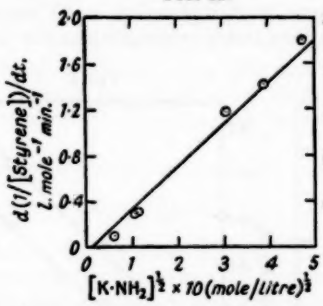
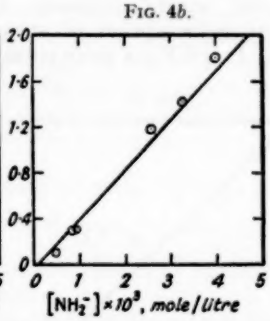


FIG. 4*b*.



(iii) The dependence of the rate of the reaction on the temperature was investigated over the temperature range −33·5° to −64° and the results are summarised in Table 8. The

TABLE 8.

Expt.	Initial $[C_8H_8]_2$, mole/l. × 10^2	$[NH_2^-]$, mole/l. × 10^3	Temp.	$10^3/T$	k''	$\log_{10} k''$
Average of KA to KF	5·75—32·4	0·87 (av.)	−33·5°	4·171	342	2·534
KB	11·9	0·92	−33·5	4·171	326	2·513
KL	10·0	0·74	−35·0	4·198	280	2·447
KM	12·95	0·90	−39·0	4·270	177	2·248
KN	10·55	0·76	−44·0	4·363	97	1·987
KP	9·77	0·74	−49·0	4·460	121	2·083
KQ	11·69	0·79	−54·0	4·562	63	1·799
KR	10·65	0·71	−59·0	4·669	46	1·663
KS	12·0	0·82	−64·0	4·780	16·5	1·218

corresponding Arrhenius line (Fig. 5) shows that the overall activation energy for the polymerisation reaction is 8·8 ± 2·0 kcal./mole.

(iv) The rate of styrene disappearance at high monomer concentrations. The linear dependence of average molecular weight on initial styrene concentration only holds up to a concentration of 0·3M-styrene and two kinetic experiments summarised in Table 9 were done at initial styrene concentrations above this value to see if the kinetic behaviour was also anomalous. In such experiments sampling and stirring were difficult, as the heavy precipitate of polymer caused the reaction mixture to assume a thick, mud-like consistency. The plots of 1/[Styrene] against time show that the reaction was initially of the second order with respect to styrene concentration, but particularly in the case of the experiment at higher styrene concentration, there was a noticeable falling off in the reaction rate after about two-thirds reaction. The

TABLE 9.

Temperature = −33·5°.

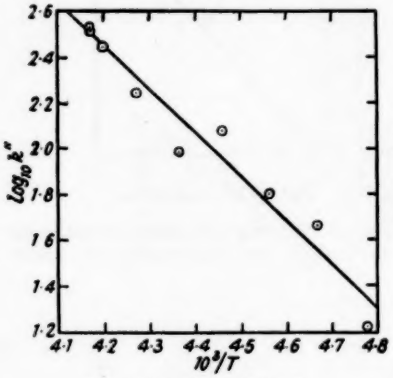
Expt.	Initial $[C_8H_8]_2$, mole/l. × 10^2	$[NH_2^-]$, mole/l. × 10^3	k''
KT	38·35	0·88	138
KU	58·1	0·81	135
Average of KA to KF	5·75—32·4	0·87 (av.)	342 (av.)

value of k'' calculated from the linear part of the plots was less than half that to be expected for the reaction at −33·5°.

Discussion

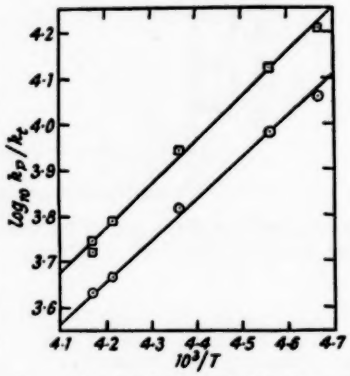
The main features of the polymerisation in dilute solutions of the reagents (up to 0·3M-styrene and 0·25M-potassium amide) may be summarised as follows. (*a*) The polymer contains one nitrogen atom per polymer molecule. (*b*) The polymer chain is saturated. (*c*) The molecular weight of polymer produced is independent of the potassium amide concentration and of the amide-ion concentration. (*d*) The molecular weight at constant conversion is independent of the potassium-ion concentration. (*e*) The molecular weight depends linearly on the initial styrene concentration up to 0·3M-styrene. (*f*) The molecular weight decreases slightly with increasing degree of conversion of monomer into polymer. (*g*) The molecular weight increases with a decrease in temperature. (*h*) The rate expression for consumption of styrene is $d[\text{Styrene}]/dt = k'[\text{Styrene}]^2[KNH_2]^{\frac{1}{2}} = k''[\text{Styrene}]^2[NH_2^-]$. (*i*) For a given potassium amide concentration the time of formation

FIG. 5.



$E = 8·8 \pm 2·0$ *kcal./mole.*

FIG. 6.



$E_p - E_t = 4·4$ *kcal./mole* (*simple equation*).
$E_p - E_t = 4·15$ *kcal./mole* (*full equation*).

of visible polymer decreases greatly with increase in potassium-ion concentration for a given potassium amide concentration. (*j*) The rate of reaction decreases with a decrease in temperature. (*k*) Consumption of potassium amide during the polymerisation is small, possibly nil (see below).

Plausible mechanisms which can be suggested for the polymerisation all involve the same initiation and propagation reactions, *i.e.* :

$$(I, a)\quad (K^+)NH_2^- + CH_2{:}CHPh \longrightarrow NH_2{\cdot}CH_2{\cdot}\overset{(-)}{C}HPh + (K^+)\quad (\textit{Initiation})$$

$$(P)\quad NH_2{\cdot}CH_2{\cdot}\overset{(-)}{C}HPh + CH_2{:}CHPh \longrightarrow NH_2{\cdot}CH_2{\cdot}CHPh{\cdot}CH_2{\cdot}\overset{(-)}{C}HPh\quad (\textit{Propagation})$$

The possibility of the alternative initiation steps

$$(I, b, \text{i})\quad (K^+)NH_2^- + CH_2{:}CHPh \longrightarrow (K^+)CH_2{:}\bar{C}Ph + NH_3$$

followed by

$$(I, b, \text{ii})\quad (K^+)\overset{(-)}{C}H_2{:}CPh + CH_2{:}CHPh \longrightarrow CH_2{:}CPh{\cdot}CH_2{\cdot}\overset{(-)}{C}HPh(K^+)$$

is unlikely, for some unsaturation would be found in the polymer chain, contrary to the experimental findings.

For the termination (*T*) three alternative reactions can be suggested :

(a) *Termination by the potassium ion.* This would involve a consumption of one molecule of potassium amide for each polymer chain. On this basis, in kinetic experiments

with an initial potassium amide concentration of the order 10^{-2}M, the consumption of potassium amide after ½ of the styrene originally present had reacted would be approximately $0{\cdot}6 \times 10^{-2}$M. The resulting change in amide-ion concentration would cause a marked curvature of the plots of 1/[Styrene] against time, but they were in nearly all cases good straight lines. In addition, experiments in which the reaction mixture was filtered after almost complete polymerisation, showed that there was little change in the potassium amide concentration in the ammonia filtrate. Though the accuracy of such experiments was not high, it was certain that any consumption of potassium amide must be very much less than one potassium amide molecule per polymer chain. Finally, termination by the potassium ion should lead to a dependence of molecular weight on the potassium-ion concentration, which did not appear experimentally.

(b) *Proton transfer from a monomer molecule, giving* $CH_2{:}\overset{(-)}{C}Ph$. The monomer anion, if formed, can react either with ammonia or with a monomer molecule, starting a second polymerisation cycle. In the latter case, as with the corresponding initiation mechanism, some unsaturation would be expected in the polymer, but none was found. As, in general, for acids of comparable strength, proton-transfer reactions in which a C–H bond is broken proceed much less easily than those involving an N–H bond, it is difficult to imagine this termination mechanism predominating over the third termination possibility (c).

(c) *Termination by proton transfer from a solvent ammonia molecule, thus* :

$$(T,c)\quad NH_2{\cdot}(CH_2{\cdot}CHPh)_n{\cdot}CH_2{\cdot}\overset{(-)}{C}HPh + NH_3 \longrightarrow NH_2{\cdot}(CH_2{\cdot}CHPh)_n{\cdot}CH_2{\cdot}CH_2Ph + NH_2^-$$

This termination mechanism does not suffer from the objections applicable to (a) and (b) and is consistent with the experimental evidence.

The effect of added potassium ions in greatly retarding the rate of formation of visible polymer, *i.e.*, in decreasing the rate of polymerisation, seems to indicate that the amide ion alone and not the potassium amide ion-pair is involved in the formation of the transition complex of the initiation step. An increase in the potassium-ion concentration for a given potassium amide concentration would greatly reduce the amide-ion concentration in solution and hence the stationary concentration of the transition complex, but is unlikely to have any great effect if the potassium ion is also present in this complex, even though salt effects are likely to be more pronounced in liquid ammonia than in water. In addition, the dependence of the rate of reaction on the square root of the potassium amide concentration, which at these concentrations is proportional to the amide-ion concentration, is also evidence in favour of the amide ion as the initiating species.

The polymerisation mechanism involving the three steps (I, *a*), (*P*), and (*T*, *c*) thus seems to be the most likely and can best be checked by comparing the experimental kinetic and molecular weight dependences on reactant concentrations with those predicted by a stationary-state treatment of the above mechanism.

The various kinetic steps in the polymerisation reaction can be represented as follows :

$$\text{Initiation}: \quad M + NH_2^- \xrightarrow{k_i} M_1^-$$

$$\text{Propagation}: \quad M_1^- + M \xrightarrow{k_p} M_2^-$$

$$M_j^- + M \xrightarrow{k_p} M^-_{(j+1)}$$

$$\text{Termination}: \quad M_r^- + NH_3 \xrightarrow{k_t} M_rH + NH_2^-$$

If it is assumed that k_p and k_t are independent of the chain length of the growing polymer, and if $M^- = \Sigma M_j^-$, application of the stationary-state condition to the concentration of active centres,

$$d[M^-]/dt = 0 = k_i[M][NH_2^-] - k_t[M^-][NH_3] \quad . \quad . \quad . \quad . \quad (1)$$

leads to

$$\frac{-d[M]}{dt} = k_i[M][NH_2^-]\left(1 + \frac{k_p[M]}{k_t[NH_3]}\right) \quad . \quad . \quad . \quad . \quad . \quad (2)$$

Under the experimental conditions $k_p[M]/k_t[NH_3]$ is generally large compared with unity, and within the accuracy of the kinetic experiments (2) can be simplified to

$$\frac{-d[M]}{dt} = \frac{k_t k_p}{k_t}\frac{[M]^2[NH_2^-]}{[NH_3]} \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad (3)$$

$$\text{If } P_r = [M_rH],\ dP_r/dt = k_t[M_r^-][NH_3]$$

and, applying the stationary-state condition $d[M_r^-]/dt = 0$, we have

$$d[M_r^-]/dt = 0 = k_p[M][M_{(r-1)}^-] - k_p[M][M_r^-] - k_t[NH_3][M_r^-] \quad . \quad (4)$$

and

$$\frac{dP_r}{dt} = \left(\frac{k_t k_t[NH_2^-][M][NH_3]}{k_p[M] + k_t[NH_3]}\right)\left(\frac{k_p[M]}{k_p[M] + k_t[NH_3]}\right)^{r-1} \quad . \quad . \quad . \quad . \quad (5)$$

Now

$$-dP_r/d[M] = (dP_r/dt) \div (-d[M]/dt)$$

hence from (2) and (5)

$$\frac{-dP_r}{d[M]} = \left(\frac{k_t^2[NH_3]^2}{(k_t[NH_3] + k_p[M])^2}\right)\left(\frac{k_p[M]}{k_p[M] + k_t[NH_3]}\right)^{r-1}$$

$$-dP_r = \int_{[M_0]}^{[M_f]}\left(\frac{k_t^2[NH_3]^2}{(k_t[NH_3] + k_p[M])^2}\right)\left(\frac{k_p[M]}{k_p[M] + k_t[NH_3]}\right)^{r-1} d[M]$$

where M_f and M_0 are respectively the final and the initial monomer concentration, *i.e.*,

$$P_r = \frac{k_t}{k_p}[NH_3]\frac{1}{r}\left[\left(\frac{k_p[M_0]}{k_p[M_0] + k_t[NH_3]}\right)^r - \left(\frac{k_p[M_f]}{k_p[M_f] + k_t[NH_3]}\right)^r\right] \quad . \quad . \quad (6)$$

Now

$$\frac{\overline{W}}{m} = v_w = \frac{\sum_{r=1}^{\infty} r^2 P_r}{\sum_{r=1}^{\infty} r P_r} \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad (7)$$

where $\overline{W}$ is the weight-average molecular weight, v_w the corresponding average chain length, and m the molecular weight of the monomer.

In the simple case of 100% polymerisation ($[M_f] = 0$), evaluation of (7) by substitution for P_r and summation gives

$$v_w = 1 + k_p[M_0]/k_t[NH_3] \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad (8)$$

Now, in purifying the polymer and freeing it from unchanged styrene, it is probable that the lower molecular weight polystyrenes will not be precipitated, but will remain in solution in the methanol–water solvent. In this connection 2-phenylethylamine, the simplest product of the polymerisation reaction, is known to be soluble in both water and methanol. As the method of purification was standardised, we may assume that only chain lengths of j and above are precipitated. Hence the expression for v_w becomes

$$v_w = \sum_{r=j}^{\infty} r^2 P_r / \sum_{r=j}^{\infty} r P_r \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad (9)$$

whence, if $[M_f] \neq 0$, substitution for P_r and summation give

$$v_w = \frac{Y^j\left(\frac{j-1}{1-Y} + \frac{1}{(1-Y)^2}\right) - Z^j\left(\frac{j-1}{1-Z} + \frac{1}{(1-Z)^2}\right)}{Y^j/(1-Y) - Z^j/(1-Z)} \quad . \quad . \quad (10)$$

where

$$Y = \frac{k_p[M_0]}{k_p[M_0] + k_t[NH_3]} \text{ and } Z = \frac{k_p[M_f]}{k_p[M_f] + k_t[NH_3]}$$

When $[M_f] = 0$ equation (10) reduces to

$$v_w = j + Y/(1-Y) = j + k_p[M_0]/k_t[NH_3] \quad . \quad . \quad . \quad . \quad (11)$$

Thus for complete polymerisation a simple linear relationship between v_w and $[M_0]$ should hold. Fig. 2 shows an approximately linear relation between v_w and $[M_0]$ up to $[M_0] \simeq$

0·3*M*. This plot contains all the values obtained, irrespective of the degree of conversion of monomer into polymer. From the treatment given above it appears that both the degree of conversion and the degree of fractionation of the polymer will affect the value of v_w and it is necessary to determine how variations in these quantities will affect the form of the dependence of v_w on $[M_0]$.

The ratio $v_w(x\%$ conversion$)/v_w(100\%$ conversion$)$ has been calculated by using different values of j in the range 1—6 for values of $x\%\{= 100([M_0] - [M_f])/[M_0]\%\}$ similar to those attained in the experiments summarised in Table 4. (In the experiments with lower initial concentrations of styrene, the percentage conversion was considerably greater than the percentage yield of polymer, owing presumably to the relatively greater proportion of low molecular weight polymer fractionated in the purification procedure.) It was found that a linear connection between v_w and $[M_0]$ should still apply to a series of experiments in which the degree of conversion was approximately the same though different from 100%, that the slope does not give a good value for k_p/k_t, but that the intercept when $[M_0] = 0$ would yield a value for j very similar to that found from a series of experiments at 100% conversion. It is noteworthy that those points which appear to be " high " in Fig. 2 were obtained from experiments in which the percentage conversion, as judged by the yield of polymer, was unduly low relatively to that obtained in experiments at similar concentrations. This positive deviation for low conversions is to be expected from the above treatment of the chain-length dependence. Equation (11) being used, the positive intercept on the molecular weight axis at $[M_0] = 0$ shows that at very low initial concentrations of monomer, the chain length of the polymer separated is 4 and hence polymer of chain length up to, but excluding, 4 is fractionated, *i.e.*, $j = 4$.

Although Fig. 2 may be taken as establishing the linear dependence of v_w on $[M_0]$ up to $[M_0] = 0{\cdot}3$ mole/litre, as the degree of polymerisation was not accurately known these results cannot be used for a satisfactory evaluation of k_p/k_t. In the experiments summarised in Table 5 the ratio $[M_f]/[M_0]$ was 0·5 in each case, and by using the full expression (equation 10) with $j = 4$ and $[M_f] = \frac{1}{2}[M_0]$, a plot of $k_p[M_0]/k_t[NH_3]$ against v_w was constructed over a suitable range of values of v_w. By interpolation in this plot it was possible to find the value of $k_p[M_0]/k_t[NH_3]$ corresponding to a given observed chain length at 50% conversion. As $[M_0]$ and $[NH_3]$ were known, the corresponding value of k_p/k_t could be found. These values at different temperatures, together with the values found by using equation (11), are summarised in Table 5. Here $[NH_3]$ is taken as 48·0 moles/litre in each case. It can be seen from Table 5 that the effect of incomplete conversion on the molecular weight is not large, as k_p/k_t values found by using equation (11), *i.e.*, assuming that the molecular weight is unaffected by the degree of conversion, are only 40% greater than those found by using the full equation (10) for 50% conversion. The plot of log k_p/k_t against $1/T$ (Fig. 6) shows that $E_p - E_t = -(4 \pm 1)$ kcal./mole, where E_p is the activation energy of the propagation reaction and E_t that of the termination reaction.

The overall kinetic expression found for the rate of disappearance of monomer is of the same form as that deduced (equation 3). Here, as in the case of the dependence of molecular weight on styrene concentrations, the similarity between the experimental and the theoretical relationships provides good confirmation for the proposed mechanism. The other mechanisms previously mentioned lead to different expressions for both the dependence of polymer-chain length and rate of disappearance of monomer on reactant concentrations and hence these mechanisms are considered to be inapplicable. It appears therefore that the overall reaction velocity constant found experimentally, k'', is equal to $k_i k_p/k_t[NH_3]$.

At the amide concentrations used, the rate expression can be written

$$\frac{-\mathrm{d}[M]}{\mathrm{d}t} = \frac{k_i k_p}{k_t} \cdot K^{\frac{1}{2}}_{\text{diss. } KNH_2} \cdot \frac{[M^2][KNH_2]^{\frac{1}{2}}}{[NH_3]}$$

and hence the overall activation energy E is given by

$$E = E_i + E_p - E_t + \tfrac{1}{2}\Delta H_{(\text{diss. } KNH_2)}$$

where E_i is the activation energy of the initiation reaction and is therefore given by

$$E_i = E - (E_p - E_t) - \tfrac{1}{2}\Delta H_{(\text{diss. } KNH_2)}$$

It has been shown above that $\Delta H_{(\text{diss. } KNH_2)} = 0 \pm 2$ kcal./mole and so from the observed overall activation energy (Fig. 5) of 9 ± 2 kcal./mole and the value of $-(4 \pm 1)$ kcal./mole for $(E_p - E_t)$, we have $E_i = 13 \pm 4$ kcal./mole.

These experimental findings can be summarised as follows: (i) The overall velocity constant $k_i k_p/k_t$ at $-33{\cdot}5° = 274$ l. mole^{-1} sec.$^{-1}$ (from $k'' = 342$, Table 7). (ii) The overall energy of activation $(E_i + E_p - E_t) = 9 \pm 2$ kcal./mole. (iii) k_p/k_t at $-33{\cdot}5° = 4{\cdot}28 \times 10^3$ (Table 5). (iv) $(E_p - E_t) = -(4 \pm 1)$ kcal./mole. (v) k_i at $-33{\cdot}5° = 6{\cdot}4 \times 10^{-2}$ l. mole^{-1} sec.$^{-1}$. (vi) $k_i = 4{\cdot}4 \times 10^{10} \exp(-13\,000/RT)$ l. mole^{-1} sec.$^{-1}$.

Although the proposed mechanism evidently holds up to initial styrene concentrations of the order 0·3M, yet the anomalously low rate of reaction and molecular weights found above this concentration may indicate that other reactions are occurring at these higher concentrations. However, the reaction solution becomes of mud-like consistency after only a few seconds' reaction, owing to the heavy precipitate of polymer formed and so the reaction medium was very different in such properties as viscosity from that obtaining at the lower concentrations of styrene. In the case of radical polymerisation, an increase in the viscosity of the medium generally results in an increase in the average molecular weight, whereas here the reverse is the case. However, in a polymerisation of ionic mechanism other factors such as a change in the dielectric constant of the medium—which, for example, might markedly affect the dissociation of potassium amide in this reaction—are also likely to affect the rates of the various reactions. It is therefore difficult to suggest any satisfactory interpretation of the anomalies observed. They cannot be ascribed to the use of an inappropriate molecular weight–intrinsic viscosity relation in calculating the relevant molecular weights, for a decrease in the intrinsic viscosity is observed on increasing the initial styrene concentration above 0·3M. In addition, the rate of disappearance of monomer also becomes unexpectedly low above this concentration.

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139. *Anionic Polymerisation. Part II.* The Acid–Base Character of Anionic Polymerisation.*

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A qualitative survey has been made of the reactivity of various anion bases in initiating the polymerisation of vinyl monomers in liquid ammonia and in diethyl ether as solvents. The observed correlation between base strength and reactivity is in accord with the anionic mechanism of these polymerisation reactions.

The relative pK of acetylene in liquid ammonia as solvent has been estimated.

IN the preceding paper a detailed mechanism has been established for the polymerisation of styrene by potassium amide in liquid ammonia. This mechanism follows that suggested by Sanderson and Hauser (*J. Amer. Chem. Soc.*, 1949, **71**, 1595) who first reported quantitative measurements in a similar system, styrene–sodium amide–liquid ammonia, and was also suggested in a preliminary communication (Evans, Higginson, and Wooding, *Rec. Trav. chim.*, 1949, **68**, 1069). It seems probable that in all such cases of anionic polymerisation of vinyl monomers the initiation reaction involves the addition of a base to a monomer molecule, forming a carbanion :

$$(X^+)B^- + >C{=}C< \longrightarrow B{-}\overset{|}{C}{-}\overset{(-)}{\underset{|}{C}}<(X^+)$$

* Part I, preceding paper.

The propagation reaction then follows :

$$B-\overset{|}{C}-\overset{(-)}{C}<(X^+) + >C=C< \longrightarrow B-\overset{|}{C}-\overset{|}{C}-\overset{|}{C}-\overset{(-)}{C}<(X^+), \text{ etc.}$$

and the termination reaction, which competes with the propagation reaction, involves the addition of a Lewis acid, *i.e.*, electron-pair acceptor, to the growing polymer chain :

$$B-[-\overset{|}{C}-\overset{|}{C}-]_n-\overset{|}{C}-\overset{(-)}{C}<(X^+) + A^+ \longrightarrow B-[-\overset{|}{C}-\overset{|}{C}-]_n-\overset{|}{C}-\overset{|}{C}-A\ (+ X^+)$$

(compare Beaman, *J. Amer. Chem. Soc.*, 1948, **70**, 3115). In the styrene–potassium amide–liquid ammonia system ($A^+ = H^+$), the termination is due to proton transfer from a solvent ammonia molecule, the conjugate acid to the catalyst base.

In the work now reported an attempt has been made to correlate qualitatively the base strength of the catalyst with its catalytic activity in the polymerisation of various vinyl monomers in liquid ammonia and in diethyl ether as solvents. All the cases dealt with here appear to fall into the class where termination is by proton addition to the growing polymer chain rather than by addition of any other electron-pair acceptor.

Liquid ammonia was used as reaction medium for certain of the experiments which were an extension of those previously reported (Evans, Higginson, and Wooding, *loc. cit.*). (With styrene as monomer and sodium anilide as initiating species there is a discrepancy between the previous and the present findings. The present experiments were done under standard conditions which differed from those previously used. The anilide ion is evidently only just an effective catalyst for the polymerisation of styrene in liquid ammonia.)

In other experiments, diethyl ether was used, since in this solvent semi-quantitative data on the strengths of weak acids have been obtained by Conant and Wheland (*J. Amer. Chem. Soc.*, 1932, **54**, 1212) and by McEwan (*ibid.*, 1936, **58**, 1124). In many ways the use of ether rather than liquid ammonia as solvent leads to a simpler interpretation of the effect of various catalyst bases. Unlike liquid ammonia, this solvent is inert and cannot enter into proton-transfer equilibria with the polymerisation catalysts. As solvent termination cannot occur in ether there are two possible termination reactions :

(1) Termination can be effected by proton transfer to the growing polymer chain from the acid conjugate to the catalyst base. For complete conversion of monomer into polymer and with no fractionation of the polymer, this leads to an expression of the weight-average molecular weight similar to that deduced for the styrene–potassium amide–liquid ammonia system under similar conditions, *viz.* :

$$\nu_w = 1 + k_p[M_0]/k_t[HB] \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad (1)$$

(For a definition of the symbols used, see preceding paper.) Unlike polymerisation in liquid ammonia, in the ether system the acid, HB, conjugate to the catalyst base is not the solvent and so the concentration of the terminating species can be varied in this solvent.

(2) In addition to the above mechanism, the termination reaction can in principle occur by proton transfer from a monomer molecule to the growing chain :

$$M_x^{(-)} + H>C=C< \longrightarrow M_xH \text{ (dead polymer)} + -\overset{(-)}{C}=C< \quad . \quad . \quad (2)$$

an alternative reaction to the propagation step

$$M_x^{(-)} + H>C=C< \longrightarrow M_{x+1}^{(-)}$$

The species $-\overset{(-)}{C}=C<$ can of course react with monomer, and commence a second polymer chain :

$$>C=C< + -\overset{(-)}{C}=C< \longrightarrow >\overset{(-)}{C}-\overset{|}{C}-\overset{|}{C}=C<$$

and thus this second termination reaction is of the chain-transfer type. In this case the chain length is independent of reactant concentrations and depends only on the ratio of k_p to k_t.

With methyl methacrylate as monomer and triphenylmethylsodium as catalyst in

ether solution an attempt was made to decide whether termination reaction (2) occurred. Triphenylmethylsodium is the most strongly basic catalyst used in the experiments in ether and the conjugate acid triphenylmethane is thus the weakest in these experiments. These conditions are likely to be the most favourable to termination by proton transfer from a monomer molecule.

In Table 1 is shown the effect of an increase in monomer concentration on the molecular weight, the concentration of triphenylmethylsodium and triphenylmethane being kept as far as possible constant. Table 2 shows, for approximately constant monomer and triphenylmethylsodium concentrations, the effect of an increase in triphenylmethane concentration on the molecular weight. Qualitatively, the increase in molecular weight with increase in monomer concentration and with decrease in triphenylmethane concentration is to be expected if termination reaction (1) occurs, but the quantitative correlation

TABLE 1.

Temp. $\simeq 20°$; $[CPh_3Na] \simeq 0{\cdot}04$ mole/l.; $[CHPh_3] \simeq 0{\cdot}04$ mole/l.

[Monomer], mole/l.	$[\eta]$	Mol. wt.*
0·43	0·0925	6,150
0·82	0·1073	7,600
1·26	0·1225	9,250
1·76	0·1382	11,000

TABLE 2.

Temp. $\simeq 20°$; $[CPh_3Na] \simeq 0{\cdot}06$ mole/l.; [Monomer] = 0·15 mole/l.

[Monomer], mole/l.	$[\eta]$	Mol. wt.*
0·01	0·1665	18,600
0·08	0·1157	8,500
0·14	0·0987	6,700

* Calculated from $[\eta]$ by using Baxendale, Bywater, and Evans's intrinsic viscosity–molecular weight relation for methyl methacrylate (*J. Polymer Sci.*, 1946, **1**, 237).

between the concentrations and the molecular weight which equation (1) predicts, *viz.*, $(\nu_w - 1) \propto [M_0]$; $(\nu_w - 1) \propto 1/[CHPh_3]$, does not appear. The dependence observed can, however, be explained on the assumption that, though termination reaction (2) does occur, reaction (1) predominates. More certain evidence that termination reaction (2) occurs only to a small extent is the absence of olefinic unsaturation in the polymer. (In polymer of chain length approximately 60 the presence of one double bond per polymer chain in one of every ten polymer molecules can be detected by bromine absorption.) It thus seems fairly certain that termination reaction (1) predominates, though reaction (2) cannot be excluded completely.

EXPERIMENTAL

Reagents.—Xanthen was prepared by Heller and Kostanecki's method (*Ber.*, 1908, **41**, 1324), and phenylacetylene by the procedure of " Organic Syntheses " (Coll. Vol. 1, p. 428). Other acids were available and were purified by the appropriate methods. Monomers were freed from stabiliser if present and purified by the usual methods. Ammonia was purified by two distillations from metallic sodium. Ether was partially purified by refluxing over metallic sodium in an atmosphere of nitrogen, followed by distillation.

Procedure.—Experiments in liquid ammonia were carried out in absence of air in the apparatus described in the preceding paper. The catalyst base solutions were prepared by adding a potassium amide solution to a slight excess of the conjugate acid. Except for butadiene, this solution was then mixed with a solution of the monomer in liquid ammonia. After about 30 minutes at $-33{\cdot}5°$ the catalyst was neutralised with ammonium chloride. After the ammonia had boiled off, polymer, if formed, was extracted with the appropriate solvent and reprecipitated in the case of methyl methacrylate and styrene. In all experiments with acrylonitrile, polymer was produced and here it was sufficient to remove unchanged monomer together with ammonium chloride and potassium chloride by solution in water. Butadiene appeared to have a low solubility in liquid ammonia, and the purified gas was condensed into the vessel containing the potassium amide catalyst solution until the undissolved liquid butadiene was present in considerable excess. After several hours the potassium amide was neutralised with ammonium chloride. In none of the experiments in liquid ammonia were traces of polymer found after the ammonia and butadiene had boiled off. Because of the low solubility of this monomer in liquid ammonia, and as negative results were obtained with potassium amide, the strongest base which could be used, experiments with other bases were not carried out.

Experiments in diethyl ether were carried out in an all-glass apparatus similar to that used for the liquid-ammonia experiments. Manometers and connecting tubes were fitted with small heating coils to prevent condensation of ether vapour. A solution of triphenylmethyl-

sodium in ether was prepared (Renfrow and Hauser, *Org. Synth.*, Coll. Vol. 2, p. 607) and the concentration was determined by titrating the alkali formed by addition of a known amount of the solution to excess of water against standard acid. With the exceptions noted below, solutions of other catalysts were prepared by adding the triphenylmethylsodium solution to a known amount of the conjugate acid of the catalyst base until a faint colour due to the red triphenylmethyl ion remained. With xanthen and fluorene the colour of the corresponding carbanions is sufficiently similar to that of the triphenylmethyl ion to make the use of this method impossible; and hence, the weight of acid present being known, the equivalent volume of triphenylmethylsodium solution was added. Solutions of sodium ethoxide and sodium methoxide were prepared by allowing a known amount of the corresponding alcohol to react with excess of sodium in ether. The solution was decanted from excess of sodium when reaction ceased. In both the experiments in ether and in ammonia the monomer concentration was approximately molar except for butadiene, and the catalyst concentration was about 0·04 M.

Polymerisation in ethereal solution at 20° occurred rapidly as compared with the slow reaction in liquid ammonia at −33·5° and appeared to be complete in about one minute. After a few minutes polymer was filtered off from the solution. If required pure for molecular-weight determination, as in the experiments with methyl methacrylate and triphenylmethylsodium, the polymer was thoroughly washed with methanol, water, and again with methanol, and finally dried in high vacuum (P_2O_5) for 48 hours. Where no polymer was visible after a few minutes, the time of standing in the presence of catalyst was extended but in no instance was slow formation of visible polymer observed. The ether was then distilled off, and the monomer remaining examined for polymer. In all cases where no visible polymer was observed, no trace of polymer was found—the polymer if formed was always insoluble in ether.

Determination of the Relative Acid Strength of Acetylene in Liquid Ammonia.—The approximate acid strength of acetylene relative to other acids can be found by similar methods to those used by Conant and Wheland (*loc. cit.*) and McEwan (*loc. cit.*). In preliminary experiments, dried acetylene gas was passed into solutions of various carbanions in liquid ammonia; the pertinent observations are summarised in Table 3.

TABLE 3.

Hydrocarbon	$pK_{rel.}$*	Colour of corresponding carbanion	Concn.	Effect of passing C_2H_2
Fluorene	25	Orange	M/50	No change
Fluorene	25	Orange	M/1000	No change
Xanthen	29	Red	M/50	Completely and rapidly decolorised
Triphenylmethane ...	33	Red	M/50	Completely and rapidly decolorised

* The $pK_{rel.}$ values are those found by Conant and Wheland (*loc. cit.*) and by McEwan (*loc. cit.*) in ethereal solution.

TABLE 4.

Temperature −33·5°.

Time, min.	Resistance, ohms		Time, min.	Resistance, ohms	
0	247	0·01M-Potassium anilide	0	259	0·01M-Sodium acetylide
10	247		10	259	
13		C_2H_2 passed for 0·5 min.	15		Aniline solution added to make test solution M/20 in NH_2Ph
14	299				
17	299				
20		More C_2H_2 passed	17	261	
21	288		22	262	
23	287		30	262	
27		More C_2H_2 passed			
28	289				
32	288				

As the acetylide ion is colourless, these results are interpreted as showing that acetylene is a stronger acid than xanthen and triphenylmethane, but weaker than fluorene. Hence, assuming that the order of acid strengths in ether is paralleled by that in ammonia (cf. Bell, "Acid–Base Catalysis," 1941, p. 108, Oxford,) we have $25 < pK_{rel.(acetylene)} < 29$. To reduce these limits, comparison with aniline was made. The anilide ion is colourless in liquid ammonia, and so a conductivity method of determining the position of equilibrium in the anilide ion–acetylene system was used. The conductivity apparatus was that previously described.

Sodium acetylide solution in liquid ammonia was prepared by passing acetylene through a 0·01M-solution of sodium in liquid ammonia for 5 minutes after the blue colour of the sodium had disappeared. (It was assumed that this procedure gave a solution containing $NaC{:}CH$ and no $NaC{:}CNa$.) Sodium anilide solution was prepared as described above. The results are summarised in Table 4.

These results suggest that, although acetylene reacts with the anilide ion, yet there is little or no reaction between the acetylene ion and aniline, *i.e.*, the equilibrium $HC{:}CH + Ph{\cdot}NH^- \rightleftharpoons HC{:}C^{(-)} + Ph{\cdot}NH_2$ is well over to the right. Thus pK (acetylene) < pK (aniline) = 27. Since pK (acetylene) > 25 (Table 3), on the above arbitrary scale of acid strength the p$K_{rel.}$ of acetylene is $\simeq$ 26.

Discussion

The experimental findings are summarised in Table 5. The absence of polymerisation may be due to two factors : either the catalyst is an insufficiently strong base to add to the monomer, or the termination reaction may be so effective that the polymer is of very short chain length and would escape detection under the experimental conditions. In ethereal solution, with the exception of sodium methoxide and ethoxide, the catalyst solutions were prepared by addition of a slight excess of triphenylmethylsodium to the conjugate acid of the catalyst base and the only acid species present is triphenylmethane. Hence, the predominating termination reaction will in all cases involve proton transfer from triphenylmethane to the growing polymer chain, which, as polymer is formed in certain cases, must be a slow reaction compared with the propagation reaction. Therefore it appears that the factor responsible for absence of polymerisation is the absence or comparative slowness of the addition of the catalyst base to the monomer. The ease of such addition would be expected to increase with an increase in the base strength of the catalyst and with an increase in the Lewis acid strength of the monomer. This is analogous to the connection between catalyst acid or base strength and catalytic power found in proton-transfer reactions (Brönsted relation). The results in Table 5(*a*) indicate that the monomers can be put in order of Lewis acid strength : acrylonitrile > methyl methacrylate > styrene $\simeq$ butadiene. This order for anionic polymerisation has also been found by Walling,

Table 5.

Acid	pK (ether)	Colour of anion	Monomers *			
			Acrylo-nitrile	Methyl methacrylate	Styrene	Butadiene
		(*a*) Ethereal solution : 20°.				
Methanol	17	Colourless	+	—	—	
Ethanol	18	Colourless	+	—	—	
Acetophenone	19	Yellow	+	—	—	—
Triphenylcarbinol	19	Green	+	—	—	
Indene	21	Yellow	+	+	—	—
Phenylacetylene	21	Colourless	+	+	—	—
Diphenylamine	23	Colourless	+	+	—	—
Fluorene	25	Red	+	+	—	—
Aniline	27	Colourless	+	—	—	—
p-Methoxyaniline	27	Colourless	+	—	—	
Xanthen	29	Red	+	+	+	+
Triphenylmethane	33	Red	+	+	+	+
		(*b*) Liquid-ammonia solution : − 33·5°.				
Ethanol	18	Colourless	+	—		
Acetophenone	19	Yellow	+	—		
Triphenylcarbinol	19	Green	+	—		
Indene	21	Yellow	+	—		
Phenylacetylene	21	Colourless	+	—	—	
Diphenylamine	23	Colourless	+	+	—	
Fluorene	25	Orange	+	—	—	
Acetylene	26	Colourless	+	+	—	
Aniline	27	Colourless	+	+	+	
Xanthen	29	Red	+	+	+	
Triphenylmethane	33	Red	+	+	+	
Ammonia	36	Colourless	+	+	+	—

* + Indicates formation of polymer; — indicates absence of polymer.

Briggs, Cummings, and Mayo (*J. Amer. Chem. Soc.*, 1950, **72**, 48) from copolymerisation studies (see also Mayo and Walling, *Chem. Reviews*, 1950, **46**, 280). It would also be expected that for each monomer there would be a definite region of the pK of the catalyst below which polymerisation would become very slow. With the exception of the anilide and the *p*-methoxyanilide ions with methyl methacrylate as monomer, this is observed. These experiments were repeated carefully with the same negative result and there appears to be no simple explanation for this surprising anomaly.

In liquid ammonia, a small amount of the acid conjugate to the catalyst base was present, and the stronger acids may act as terminating species in addition to the solvent ammonia. However, the general picture is similar to that found in ether. Polymerisation was not found with butadiene, though this may be connected with the low solubility of this monomer in liquid ammonia. The only anomaly appears to be the carbanion formed from fluorene, which does not polymerise methyl methacrylate, though the apparently weaker base, the anilide ion, was effective.

In connection with these anomalies it should be emphasised that only an approximate correlation can be expected between the strength of a base and its effectiveness as a polymerisation catalyst. This correlation is in principle subject to the limitations of the Brönsted relation itself; for example, this relation often breaks down completely if applied to a series of catalysts in which the atom to which the acid hydrogen is attached changes, or in which a profound alteration in the structure of the catalyst as a whole occurs. This effect is likely to be accentuated here, for unlike the proton-transfer reactions to which the Brönsted relation applies, the bond formed in the polymerisation reaction is a bond between the catalyst and a carbon atom as distinct from a bond between the catalyst and hydrogen. In addition, steric effects are likely to be more marked than those found in proton-transfer reactions.

As only a qualitative measure of the reaction rate has been considered, *i.e.*, a reasonably rapid rate of polymerisation on the one hand and extremely slow or zero reaction on the other, fairly large deviations from a strict correlation between base strength and catalyst activity will generally pass unnoticed. Thus there appear to be relatively few catalysts for which the catalyst activity cannot be inferred from the corresponding pK value. Were more quantitative rate measurements available, however, it is probable that an exact parallelism between catalyst reactivity and base strength would not be found.

Colour of Polymers.—Though the poly(methyl methacrylate), polystyrene, and polybutadiene formed were in almost every case colourless, it is of interest that with all catalysts the polyacrylonitrile was orange-yellow and was soluble in liquid ammonia to give a yellow solution. Unlike polyacrylonitriles prepared by other methods, the yellow polymer was sparingly soluble in pyridine and in acetone. It is possible that the polymer, even though solid, was of very low molecular weight. The colour, which was permanent in air and partly retained even on solution in concentrated nitric acid followed by precipitation with water, suggests the presence of conjugated double bonds. This implies that the cyano-group may take part in the polymerisation, and that the polymer may contain groupings such as $CH_2{:}CH{\cdot}C{:}N{\cdot}C(CH{:}CH_2){:}N{\cdot}$.

Another observation was that the polymer formed from both acrylonitrile and methyl methacrylate with the acetylide ion as initiating species was highly coloured and the colour was again permanent. The polyacrylonitrile was brick-red in colour as distinct from the usual yellow to orange, while the poly(methyl methacrylate) was yellow, though in all other cases this polymer was white. Possibly the acetylene also present copolymerised to some extent with these monomers and again gave rise to conjugated double bonds in the polymer. No evidence was obtained for the polymerisation of acetylene itself in liquid ammonia.

Our thanks are offered to Professor M. G. Evans, F.R.S., for advice and encouragement in the work described in this and the preceding paper, and to Messrs. Courtaulds Ltd. for a grant to one of us (N. S. W.).

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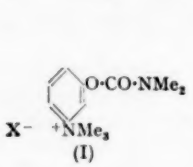
140. *The Synthesis of Neurotropic and Musculotropic Stimulators and Inhibitors. Part V.* Derivatives of Aminophenyl Phosphates as Anticholinesterases.*

By K. J. M. Andrews, F. R. Atherton, F. Bergel, and A. L. Morrison.

A number of (dialkyl phosphato)-*N*-dimethylanilines (Table 2) have been prepared by condensing dimethylaminophenols with the appropriate dialkyl chlorophosphonate. While most of these tertiary bases were stable to heat, the *m*-dimethylamino-homologue readily formed the corresponding betaine (XI). The quaternary salts (Table 3) were found to be potent inhibitors of cholinesterase.

m-(Ethyl diethylaminophosphonato)-*N*-trimethylanilinium methyl sulphate (VII) and *m*-(ethyl diethylaminophosphinato)-*N*-trimethylanilinium methyl sulphate † (VIII) were made by similar methods; they were less active as enzyme antagonists.

The first group of synthetic compounds found to be potent inhibitors of cholinesterase was that of the quaternary salts of *m*-dialkylaminophenyl carbamates (cf. Stedman, *Biochem. J.*, 1926, **20**, 719; Aeschlimann and Reinert, *J. Pharmacol.*, 1931, **43**, 413). One member of this group has found wide clinical application and is known as " Prostigmin " or neostigmine (I).



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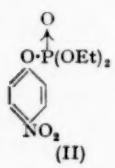

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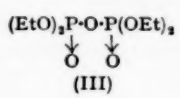

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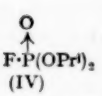

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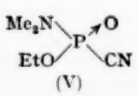

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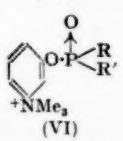

(VI)

In a search for insecticides, Schrader in Germany (B.I.O.S. Final Report, 1947, WO 714) prepared many organic phosphorus compounds which were subsequently shown to be powerful inhibitors of cholinesterase. Most of these compounds were neutral phosphates containing a labile linkage either of an ester [*e.g.*, E 600 (II)] or an anhydride [*e.g.*, tetraethylpyrophosphate (III)] type. Certain fluoro- and cyano-derivatives of phosphorus were also found to be very active, di*iso*propyl fluorophosphonate (IV) (Chapman and Saunders, *J.*, 1948, 1010) and ethyl cyanodimethylaminophosphinate (V) (Holmstedt, *Acta Phys. Scand.*, 1951, **25**, Suppl. 90) being among the most powerful.

In discussions with Drs. Burgen, Hobbiger, and Keele of the Department of Pharmacology, Middlesex Hospital Medical School, it was agreed that it would be of particular interest to study the anticholinesterase properties of a homologous series of compounds with general formula (VI). Such compounds are obviously closely related to neostigmine and also fulfil the conditions laid down by Schrader as necessary for an insecticide and now known to be equally valid for an active anticholinesterase compound. They would differ from all other known anticholinesterase phosphates in having a quaternary group and this could be expected to influence their physiological properties.

The first compound envisaged was *m*-(ethyl diethylaminophosphonato)-*N*-trimethylanilinium methyl sulphate (VII) which was prepared by condensing *m*-dimethylaminophenol with ethyl chlorodiethylaminophosphinate (prepared according to Michaelis,

* Part IV, *J.*, 1950, 2887. † For nomenclature, see *J.*, 1951, 1868.

Annalen, 1902, **326**, 129) and quaternising the resultant tertiary base with methyl sulphate. This compound and *m*-ethyldiethylaminophosphinato-*N*-trimethylanilinium methyl sulphate (VIII), made in a similar way from chloro-diethylamino-ethylphosphine oxide, were found to be less potent than neostigmine as cholinesterase inhibitors.

Chloro-diethylamino-ethylphosphine oxide was obtained by the reaction of diethylamine with excess of dichloro-ethylphosphine oxide. Compounds of this type with nitrogen, carbon, and halogen atoms attached to the same phosphorus atom have not been reported previously. Dichloro-ethylphosphine oxide was conveniently produced by treating ethylphosphonic acid (Kosolapoff, *J. Amer. Chem. Soc.*, 1945, **67**, 1180) with phosphorus pentachloride. In this and other experiments we have found it expedient to destroy excess of phosphorus pentachloride with sulphur dioxide. Phosphorus oxychloride and thionyl chloride are formed and these can be removed by distillation. This technique, which does not seem to have been applied previously, should prove equally convenient in other instances.

The next groups of compounds investigated were the *m*-(dialkyl phosphato)-*N*-dimethylanilines (IX) and the corresponding *N*-trimethylanilinium methyl sulphates (X).

The tertiary bases (IX; R = Me, Et, Pr^{i}, Bu^{n}, and Bu^{s}) were made by condensing *m*-dimethylaminophenol with the dialkyl chlorophosphonates, which were prepared according to Atherton, Howard, and Todd (*J.*, 1948, 1106) from the corresponding dialkyl phosphites (McCombie, Saunders, and Stacey, *J.*, 1945, 380).

Most of the *m*-(dialkyl phosphato)-*N*-dimethylanilines we have examined are thermally stable under the conditions required to distil them. The dimethyl homologue, however, partly decomposed during distillation to a non-volatile crystalline compound, soluble in alcohol and water but insoluble in ether. These properties, together with the analysis, show the material to be the betaine $Me_3\overset{+}{N}\cdot C_6H_4\cdot O\cdot P(O^-)(=O)OMe$. In order to prepare this betaine in a more nearly quantitative yield, the undistilled ester was heated, whereupon it quickly solidified to a crystalline mass. Crystals of the betaine are deposited in the distilled ester after storage for a few weeks, showing that this rearrangement also occurs slowly at room temperature.

The formation of quaternary salts from tertiary amines and phosphoric esters has been reported by Baddiley, Clark, Michalski, and Todd (*J.*, 1949, 815), who found that, although neutral phosphoric esters containing an arylmethyl group quaternised readily with tertiary bases, triethyl phosphate showed little tendency to react. The facile quaternary salt formation we have observed from a methyl ester may be due both to the superior lability of methyl groups and to the reaction's probably being intramolecular.

The group of compounds represented by (X; R = Me, Et, Pr^{i}, Bu^{n}, Bu^{s}) were prepared by quaternising the tertiary bases with methyl sulphate. As a representative of the *p*-series, *p*-(diethyl phosphato)-*N*-dimethylaniline and its methosulphate were made in a similar manner.

The anticholinesterase activity of these substances *in vitro* against the esterases of red blood-cells and serum, and their activity *in vivo*, have been investigated by Burgen and Hobbiger (*Brit. J. Pharmacol.*, 1951, **6**, 593). From their results, it appears that these "phosphostigmines" are very potent cholinesterase inhibitors, the quaternary derivatives being more potent than the tertiary bases, and the *m*- more potent than the *p*-compounds. Compared with neostigmine, which inhibits 50% of "true" cholinesterase at a molecular concentration of $1{\cdot}14 \times 10^{-7}$ and "pseudo" esterase at $6{\cdot}9 \times 10^{-7}$, the (dimethyl phosphato)trimethylanilinium methyl sulphate achieves the same degree of inhibition at

$7{\cdot}5 \times 10^{-8}$ and $6{\cdot}3 \times 10^{-9}$, respectively. The other interesting indication which emerges from Burgen and Hobbiger's investigations (*loc. cit.*) is that the alkyl groups of the phosphato-residue seem to influence the kinetics governing the action of these substances with the enzyme system, as shown by the different rates of reactivation of the enzyme. In this respect, the diethyl and the di*iso*propyl phosphates bear a noteworthy resemblance to TEPP and DFP which, respectively, carry the same alkyl groups.

Whatever the mechanism of interaction between the cholinesterases and their inhibitors may eventually prove to be, the stability of the phosphates in aqueous solution may have some bearing. Measured by loss of inhibitory power and toxicity, results which we owe to Dr. Hobbiger and Mr. M. W. Parkes, the percentage hydrolysis shows differences in stability between the various dialkyl homologues, as given in Table 3.

Experimental

Table 1. *Dialkyl chlorophosphonates,* $(RO)_2PCl{\rightarrow}O$, *prepared according to Atherton, Howard, and Todd* (*J.*, 1948, 1106) *by the action of sulphuryl chloride on the dialkyl phosphites in* CCl_4 *at* 35°.

R	B.p./mm.	n	Yield, %
Me	78—80°/18	1·4115 (22°)	61
Et	84—85°/10	1·4162 (23°)	87
Pr^i	82—84°/10	1·4169 (21°)	82
Bu^n	86—87°/0·5	1·4298 (21°)	85
Bu^s	66—67°/0·7	1·4272 (22°)	80

m-(*Dimethyl Phosphato*)-N-*dimethylaniline.*—*m*-Dimethylaminophenol (6·85 g., 0·05 mole) was dissolved in ethanolic sodium ethoxide (1·25 g., 0·055 mole, in 60 ml. of ethanol) under nitrogen, and dimethyl chlorophosphonate (8 g., 0·055 mole) was run in dropwise during a few minutes. The reaction mixture was heated under reflux for 1 hour and then set aside overnight. The precipitated sodium chloride was filtered off (3·1 g.) and the alcohol was evaporated from the filtrate. A dark oil remained; it was dissolved in carbon tetrachloride, and the solution was extracted three times with 0·5N-sodium hydroxide and three times with water. After filtration of the carbon tetrachloride solution, it was dried (Na_2SO_4) and filtered, and the carbon tetrachloride evaporated *in vacuo*. The residual oily *base* (50%), distilled in a high vacuum, had b. p. $97°/2{\cdot}3 \times 10^{-3}$ mm. A considerable residue was obtained, which was soluble in alcohol and insoluble in ether. Several recrystallisations from alcohol–ether gave the (*methyl phosphato*)-N-*trimethylanilinium betaine*, m. p. 219—221° (Found: N, 5·4; P, 13·1. $C_{10}H_{16}O_4NP$ requires N, 5·7; P, 12·6%) (see also below).

The *diethyl-*, *di*iso*propyl-*, *di*-n-*butyl-*, and *di*-sec.-*butyl-phosphato*-bases were prepared similarly (cf. Table 2), but there was no appreciable residue on distillation.

Table 2. (*Dialkyl phosphato*)-N-*dimethylanilines* (cf. IX).*

Alkyl	B.p./mm.	n_D	Found, % N	Found, % P	Formula	Required, % N	Required, % P
Me	97°/2·3 × 10^{-3}	1·5237 (21·5°)	5·8	12·5	$C_{10}H_{16}O_4NP$	5·7	12·6
Et	106°/10^{-4}	1·5110 (22°)	5·4	10·6	$C_{12}H_{20}O_4NP$	5·1	11·3
Pr^i	100—105°/3·7 × 10^{-4}	1·5000 (21°)	5·0	10·3	$C_{14}H_{24}O_4NP$	4·7	10·3
Bu^n	138—140°/2·3 × 10^{-4}	1·4990 (21°)	4·5	9·3	$C_{16}H_{28}O_4NP$	4·25	9·4
Bu^s	119—124°/2·5 × 10^{-4}	1·4985 (20°)	4·8	8·2	$C_{16}H_{28}O_4NP$	4·25	9·4
Et †	122—128°/5 × 10^{-5}	1·5098 (20°)	5·5	10·6	$C_{12}H_{20}O_4NP$	5·1	11·3

* All *m*-compounds, except that marked † which is the *p*-isomer.

Table 3. (*Dialkyl phosphato*)-N-*trimethylanilinium Methyl Sulphates* (cf. X).*

Alkyl	M. p.	Found, % N	Found, % P	Formula	Required, % N	Required, % P	Hydrolysis (%) ‡
Me	86—88°	3·8	8·3	$C_{12}H_{22}O_6NSP$	3·8	8·3	83
Et	105—107	4·0	7·2	$C_{14}H_{26}O_6NSP$	3·5	7·8	55
Pr^i	82—84	4·1	7·5	$C_{16}H_{30}O_6NSP$	3·4	7·25	37
Bu^n	98—100	4·4	6·4	$C_{18}H_{34}O_6NSP$	3·1	6·8	—
Bu^s	90—92	3·2	6·0	$C_{18}H_{34}O_6NSP$	3·1	6·8	—
Et †	80—81	3·2	7·8	$C_{14}H_{26}O_6NSP$	3·5	7·8	20

* All *m*-compounds, except that marked † which is the *p*-isomer.
‡ After 500 hours in 1% w/v aqueous solution at 45°.

m-(*Dimethyl phosphato*)-N-*trimethylanilinium Methyl Sulphate.*—To a solution of *m*-dimethylphosphato-*N*-dimethylaniline (1·8 g.) in dry benzene (6 ml.), methyl sulphate (1 ml.) was added and the mixture was set aside for 29 hours at room temperature. The quaternary *salt* crystallised, and further crystallisation occurred on addition of dry ether. It was collected by filtration, dried, and recrystallised twice from alcohol–ethyl acetate–ether, then having m. p. 86—88° (yield, 66%).

The *diethyl-*, *diiso*propyl-, *di*-n-*butyl-*, and *di*-sec.-*butyl-phosphato*-homologues were prepared similarly (cf. Table 3).

m-(*Methyl Phosphato*)-N-*trimethylanilinium Betaine.*—*m*-Dimethylaminophenol (13·7 g.) was dissolved in ethanolic sodium ethoxide (2·5 g. of sodium; 100 ml. of dry ethanol), and dimethyl chlorophosphonate (16 g.) was added dropwise, in a nitrogen atmosphere. The reaction mixture was refluxed for 15 minutes and then set aside for 15 hours. The precipitated sodium chloride was filtered off and the solvent was evaporated *in vacuo*. A dark residue remained which was dissolved in carbon tetrachloride and washed twice with water, twice with 0·5N-sodium hydroxide and finally twice with water. After drying of the solution, the carbon tetrachloride was evaporated *in vacuo* and the residue finally stripped at 100°/0·3 mm. A dark oil remained which was heated from 125° to 160° during 30 minutes. It had by then solidified to a buff-coloured crystalline mass, which was recrystallised by dissolution in methanol and addition of ethanol, followed by ether, until the solution was turbid. Crystallisation then took place when the solution was kept in the refrigerator (yield, 6·7 g.; m. p. 213—215°). A further recrystallisation gave colourless crystals (4·3 g.), m. p. 218—220°. From the first mother-liquors a second crop (4·3 g.) was obtained, having m. p. 215—217° (Found: N, 5·8; P, 11·8%).

m-(*Ethyl Diethylaminophosphonato*)-N-*dimethylaniline.*—To ethanolic potassium ethoxide, prepared by adding potassium (1·45 g.) to dry ethanol (80 ml.), was added *m*-dimethylaminophenol (4·1 g.) in a nitrogen atmosphere. When a clear solution had been obtained, ethyl chloro-diethylaminophosphinate (7·44 g.) was added with stirring. There was immediate precipitation of potassium chloride, and the reaction mixture was heated under reflux for 1½ hours, then set aside overnight. The potassium chloride was filtered off and the alcohol evaporated. The residue was dissolved in carbon tetrachloride (50 ml.), and the solution washed three times with N-sodium hydroxide and twice with water. After drying (K_2CO_3) of the carbon tetrachloride solution, the solvent was evaporated *in vacuo*, to give a brown oil which was distilled; the fraction (72%), b. p. 114—118°/10^{-4} mm., was collected. The *base*, redistilled, had n_D^{22} 1·5149 (Found: N, 9·1; P, 10·4. $C_{14}H_{25}O_3N_2P$ requires N, 9·3; P, 10·3%).

The *methosulphate*, prepared in dry benzene, was an oil which could not be induced to crystallise. It was analysed after several precipitations from alcohol with ether, and, finally, stripping at 0·5 mm. (Found: N, 4·9; P, 6·3. $C_{16}H_{31}O_7N_2PS$ requires N, 6·6; P, 7·3%).

Dichloro-ethylphosphine Oxide.—The crude ethylphosphonic acid obtained by hydrolysing dibutyl ethylphosphonate (199·5 g., 0·9 mole) with concentrated hydrochloric acid for 16 hours and evaporating the reaction mixture to dryness, finally under oil-pump vacuum, was dissolved in chloroform (500 ml.). To the stirred solution, phosphorus pentachloride (625 g., 3 moles) was added in portions during ¾ hour. After a further 15 hours' stirring at room temperature, the reaction was completed by 1 hour's refluxing. Excess of phosphorus pentachloride was then destroyed by passing a stream of sulphur dioxide through the ice-cold mixture for several hours. The solution was placed under vacuum to remove dissolved gases and was then evaporated *in vacuo*, and the residue fractionated *in vacuo* through a short column equipped with a stillhead with controllable reflux-ratio. The main fraction (104 g., 78·5%) consisted of *dichloro-ethylphosphine oxide*, b. p. 70—72°/14—15 mm., n_D^{20} 1·4659 (Found: Cl, 48·8. $C_2H_5OCl_2P$ requires Cl^-, 48·3%).

Chloro-ethyl-diethylaminophosphine Oxide.—A solution of diethylamine (36·5 g., 0·5 mole) in light petroleum (150 ml.; b. p. 40—60°) was slowly added during 3 hours to a stirred solution of dichloro-ethylphosphine oxide (49 g., 0·33 mole) in light petroleum (250 ml.; b. p. 40—60°) cooled in ice–salt. After a further hour's stirring at room temperature, the mixture was kept overnight. The precipitated solid was filtered off and washed with light petroleum, the filtrate was evaporated, and the residue distilled in a vacuum. The main fraction (32·3 g.), b. p. 110—124°/10 mm., was redistilled, giving 28·7 g. (63%) of *chloro-ethyl-diethylaminophosphine oxide*, n_D^{20} 1·4669 (Found: N, 8·0; P, 15·7; Cl^-, 18·4. $C_6H_{15}ONClP$ requires N, 7·6; P, 16·9; Cl, 19·4%).

m-(*Ethyl Diethylaminophosphinato*)-N-*dimethylaniline.*—*m*-Dimethylaminophenol (6·85 g.) was added to ethanolic sodium ethoxide (1·42 g. of sodium; 80 ml. of dry ethanol) in a nitrogen atmosphere, and chloro-ethyl-diethylaminophosphine oxide (11·3 g.) was added with stirring.

Procedure as for the preparation of the phosphonato-compound given above gave the *base* (78%), b. p. 132—134°/2·8 × 10^{-4} mm., n_D^{20} 1·5295 (Found: N, 9·8; P, 10·2. $C_{14}H_{25}O_3N_2P$ requires N, 9·9; P, 10·9%).

The authors are indebted to Drs. Hobbiger and Keele for very helpful co-operation, and to Mr. Whiting for technical assistance.

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[*Received, October 18th,* 1951.]

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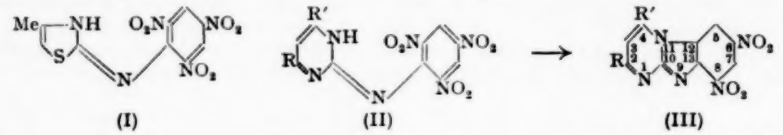
141. *New Syntheses of Heterocyclic Compounds. Part XVI.* Some Further Observations on Ring Closures involving Loss of Nitrous Acid.*

By S. S. BERG and V. PETROW.

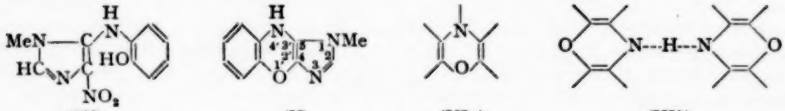
Study of the picryl derivatives of 2-amino-4-methylthiazole, 8-amino-1 : 2 : 3 : 4-tetrahydrocarbazole, 1-aminocarbazole, 2-amino-, 2-amino-6-methyl-, and 2 : 4-diamino-6-methyl-pyrimidine has revealed that only those derived from 2-aminopyrimidine undergo ring closure by loss of nitrous acid. *Inter alia* it was observed that reaction of 2 : 4 : 6-trinitroanisole with 2-aminopyridine, 2-aminothiazole, and 2-aminopyrimidine, in the presence of fused sodium acetate, leads to formation of the corresponding 2-*N*-methyl-*N*-picrylamino-derivatives.

Removal of nitrous acid from 5-*o*-hydroxyanilino-1-methyl-4-nitroglyoxaline (IV) furnished a blue derivative of (V) for which the azyl (VI*a*) or azhydrin (VI*b*) structure is proposed.

THE facile synthesis of dinitrophenoxazine from picryl chloride and *o*-aminophenol in the presence of alkali (Turpin, *J.*, 1891, 722) has formed the basis of many preparations of heterocyclic compounds of various types. By this reaction, or modifications thereof



(I) (II) (III)



(IV) (V) (VI*a*) (VI*b*)

phenothiazines (Kehrmann, *Ber.*, 1899, **32**, 2603), phenazines (Kehrmann and Messinger, *Ber.*, 1893, **26**, 2372; Leemann and Grandmougin, *Ber.*, 1908, **41**, 1308), phenoxadiazines (Plazek, *Rocz. Chem.*, 1936, **16**, 504; Petrow and Rewald, *J.*, 1945, 313), phenothiadiazines (*idem*, *J.*, 1946, 588), diazafluorenes (Morgan and Stewart, *Chem. and Ind.*, 1937, 670), and triazafluorenes (Ochiai and Yanai, *J. Chem. Soc., Japan*, 1940, **60**, 192; Petrow and Saper, *J.*, 1946, 588) have been prepared, in many cases in extremely good yield. The extension of the reaction to such compounds as aminothiazole and aminocarbazole forms the subject of the present communication.

Attempts to condense picryl chloride with 2-aminothiazole proved unsuccessful. 2-Amino-4-methylthiazole, in contrast, readily gave 2 : 3-dihydro-4-methyl-2-picryliminothiazole (I), but the ring closure of this compound could, unfortunately, not be effected.

Ochiai and Yanai (*loc. cit.*) had described the condensation of picryl chloride with 2-amino-, 2-amino-6-methyl-, and 2 : 4-diamino-6-methyl-pyrimidine, and the cyclisation of the resulting picryl derivatives (II) to the corresponding 6 : 8-dinitro-1 : 9 : 11-triaza-

* Part XV, *J.*, 1952, 334.

fluorenes (III). In our hands, however, the high yields claimed by the Japanese authors for the cyclisation could not be reached, in spite of much systematic study of the reaction conditions. Whilst, therefore, the reduction of 6 : 8-dinitro-, 2-methyl-6 : 8-dinitro-, and 4-acetamido-2-methyl-6 : 8-dinitro-1 : 9 : 11-triazafluorene to the corresponding 6 : 8-diamino-derivatives was successfully accomplished, further extension of the work was not undertaken. *Inter alia*, the observation was made that whereas reaction of 2 : 4 : 6-trinitroanisole (cf. Messlin and Bau, *Helv. Chim. Acta*, 1919, **2**, 295) with 2-aminopyrimidine in methanol leads to 2-aminopyrimidine picrate, reaction in the presence of fused sodium acetate gives 2-*N*-methylpicrylaminopyrimidine. The new reaction appears to possess some general character, as both 2-aminothiazole and 2-aminopyridine behave in the same way, giving 2-*N*-methylpicrylaminothiazole and 2-*N*-methylpicrylaminopyridine, respectively. The structure of the latter product was confirmed by direct comparison with authentic material (Morgan and Stewart, *J.*, 1938, 1298). Ethyl picrate behaved in the same way, yielding 2-*N*-ethylpicrylaminopyridine with 2-aminopyridine. 2 : 4 : 6-Trinitrodiphenyl ether similarly gave 2-*N*-phenylpicrylaminopyridine, though in poor yield.

8-Picrylamino-1 : 2 : 3 : 4-tetrahydrocarbazole and 1-picrylaminocarbazole were readily prepared by reaction of the corresponding bases with picryl chloride in benzene solution in the presence of fused sodium acetate, but could not be cyclised under a variety of experimental conditions. The result is particularly surprising in the latter case, since it bears a close resemblance to that of 2-picrylaminodiphenylamine, cyclisation of which proceeds with great facility (Kehrmann and Messinger, *loc. cit.*).

Some interesting results were obtained during experiments on the preparation of benzoxazinoglyoxaline. 5-Chloro-1-methyl-4-nitroglyoxaline (Sarason and Wegmann, *Helv. Chim. Acta*, 1924, **7**, 713) condensed smoothly with *o*-aminophenol in ethanol in the presence of fused sodium acetate and potassium iodide, to give 1-methyl-4-nitro-5-*o*-hydroxyanilinoglyoxaline (IV) in *ca.* 50% yield. Ring closure of this compound presented initial difficulty. It was ultimately found that ethanolic diethylamine at 120° led to a low yield of a brilliant blue crystalline compound of empirical formula *ca.* $C_{10}H_7ON_3$. Formulation of this product as 1-methylbenzoxazino(2′ : 3′-4 : 5)glyoxaline (V), though supported by analytical data, is hardly feasible in view of the intense blue colour of the compound. At the same time, the structural characteristics of (V) impose restrictions on the existence of quinonoid forms. It is, therefore, suggested that this product be assigned the free-radical azyl structure (VI*a*) or the " azhydrin " structure (VI*b*). Of these, the latter is preferred in view of the marked insolubility of the compound in the usual solvents.

The formation of blue azyl and azhydrin structures has previously been recorded in the dihydrophenazine series, to which (V) bears a formal resemblance. Thus McIlwain (*J.*, 1937, 1704) has shown that 3-cyano-5 : 10-dihydro-5-methylphenazine undergoes ready oxidation to the stable blue free radical 2-cyano-5 : 10-dihydro-10-methylphenaz-5-yl. Again, Clemo and McIlwain (*J.*, 1934, 1991; 1935, 738) have found that admixture of phenazine and dihydrophenazine in equimolar amounts leads to the formation of a crystalline blue " phenazhydrin " which contains the system of hydrogen bonds shown in (VI*b*). The formulation of the blue product in this manner is further supported by the observation that reduction with zinc dust in concentrated sulphuric acid leads to a pink compound which is presumably a reduced form. Its isolation and characteristics have not, however, proved possible, in view of the extreme facility with which it reverts to the blue product in the presence of traces of air.

Experimental

M. p.s are uncorrected. Microanalyses are by Mr. S. Bance, B.Sc., A.R.I.C.

Reaction of Picryl Chloride and 2-Aminothiazole.—Picryl chloride (2·5 g.) was added to 2-aminothiazole (2·0 g.) in dry benzene (30 ml.), and the solution heated under reflux for 5 hours. Addition of light petroleum (30 ml.; b. p. 40—60°) to the cooled solution leads to the separation of a *complex* (2·3 g.), m. p. 89—110°, of 2-aminothiazole picryl chloride (Found : N, 19·6; Cl, 9·7. $C_3H_4N_2S,C_6H_2O_6N_3Cl$ requires N, 20·1; Cl, 10·2%).

2 : 3-*Dihydro-4-methyl-2-picryliminothiazole* (I), prepared by treating a boiling solution of 2-amino-4-methylthiazole (10 g.) in toluene (100 ml.) with picryl chloride (11 g.) in toluene

(100 ml.) and refluxing the whole for 3 hours, formed crimson prisms (10·2 g.), m. p. 184—185°, from benzene (Found: N, 21·6; S, 10·1. $C_{10}H_7O_6N_5S$ requires N, 21·5; S, 9·8%). Attempts at ring closure included treatment with potassium hydroxide–methanol under reflux, phenol–nitrobenzene under reflux, redistilled dimethylaniline at 200°, and sublimation at 170—175°/0·03 mm.

6 : 8-*Diamino*-1 : 9 : 11-*triazafluorene*.—6 : 8-Dinitro-1 : 9 : 11-triazafluorene (500 mg.) in warm methanol (25 ml.) was reduced catalytically at atmospheric pressure with Adams's platinum oxide catalyst (100 mg.). Reduction was complete in 1 hour, the colour of the solution changing to green. 6 : 8-*Diamino*-1 : 9 : 11-*triazafluorene*, isolated in the usual way, formed green prisms (200 mg.), m. p. >300° (Found: C, 60·0; H, 4·3; N, 35·4. $C_{10}H_9N_5$ requires C, 60·3; H, 4·5; N, 35·2%).

6 : 8-*Diamino*-2-*methyl*-1 : 9 : 11-*triazafluorene dihydrochloride*, prepared by reduction of the corresponding dinitro-compound (400 mg.) in warm methanol (20 ml.) containing dilute hydrochloric acid (2 ml.) at 35—45° in the presence of Adams's catalyst (100 mg.) for 3 hours, formed pale yellow prisms (150 mg.), m. p. >300°, from 3N-hydrochloric acid (Found: N. 24·6; Cl, 24·3. $C_{11}H_{11}N_5$,2HCl requires N, 24·6; Cl, 24·8%).

4 : 6 : 8-*Triamino*-2-*methyl*-1 : 9 : 11-*triazafluorene trihydrochloride*, prepared by reduction of the acetamido-dinitro-compound (8 g.) in warm methanol (2500 ml.) over Adams's catalyst (1 g.) for 1 hour, formed pink prisms (3·2 g.), m. p. >300°, from dilute hydrochloric acid (Found: N, 25·1; Cl, 31·2. $C_{11}H_{13}N_6$,3HCl requires N, 25·0; Cl, 31·6%).

Attempts to Condense Bromo-2 : 4-*dinitrobenzene with* 2-*Amino*-4-*methylpyridine*.—(*a*) Reaction was not observed when 2-amino-4-methylpyridine (1 g.), 1-bromo-2 : 4-dinitrobenzene (2·5 g.), fused sodium acetate, and anhydrous toluene (20 ml.) were heated under reflux for 5 hours.

(*b*) 2-Amino-4-methylpyrimidine (2 g.) and 1-bromo-2 : 4-dinitrobenzene (12 g.) failed to condense at 120—125° during 3 hours, but reacted explosively with total charring when the temperature was raised to 150°.

(*c*) Condensation could not be effected by heating the components under reflux in *cyclo*hexanol in the presence of a trace of copper bronze for 5 hours.

Condensation Reactions employing 2 : 4 : 6-*Trinitroanisole*.—(*a*) Reaction of 2 : 4 : 6-trinitroanisole (2·5 g.) with 2-aminopyrimidine (1 g.) in dry methanol (15 ml.) under reflux for 45 minutes produced 2-aminopyrimidine picrate (2·7 g.), m. p. 234—235°, alone or in admixture with an authentic specimen.

(*b*) 2-N-*Methylpicrylaminopyrimidine* (0·6 g.), yellow prisms or rhombs (from acetic acid or benzene), m. p. 225—226° (Found: C, 41·1; H, 2·75; N, 26·2. $C_{11}H_8O_6N_6$ requires C, 41·2; H, 2·5; N, 26·2%), was obtained by heating trinitroanisole (2·4 g.), 2-aminopyrimidine (0·95 g.), fused sodium acetate (3 g.), and dry methanol (40 ml.) under reflux for 5 hours.

(*c*) 2-N-*Methylpicrylaminothiazole* (700 mg.), similarly prepared from 2-aminothiazole (1·0 g.), formed blood-red rhombs, m. p. 206—208°, from dry benzene (Found: C. 36·9; H, 2·5; N, 21·6; S, 10·2. $C_{10}H_7O_6N_5S$ requires C, 36·9; H, 2·2; N, 21·5; S, 10·2%).

(*d*) 2-*N*-Methylpicrylaminopyridine formed red prisms, m. p. 240—242°, from acetic acid (Found: C, 45·2; H, 2·6; N, 21·7. Calc. for $C_{12}H_9O_6N_5$: C, 45·1; H, 2·8; N, 21·9%), not depressed on admixture with an authentic specimen (Morgan and Stewart, *loc. cit.*).

(*e*) Reaction of trinitroanisole (12 g.) with 2-picrylaminopyridine (1·5 g.) and fused sodium acetate (1·5 g.) in dry methanol (20 ml.) for 5 hours under reflux gave the *N*-methyl derivative (200 mg.), m. p. 242—243°, not depressed on admixture with a sample prepared as under (*d*).

(*f*) *N*-Methylation of carbazole and diphenylamine could not be effected.

2-N-*Ethylpicrylaminopyridine*, similarly prepared from ethyl picrate (2·6 g.) and 2-aminopyridine (950 mg.), formed red rhombs (500 mg.) (from acetic acid), m. p. 234—236° (Found: C, 47·0; H, 3·5; N, 20·9. $C_{13}H_{11}O_6N_5$ requires C, 46·8; H, 3·3; N, 21·0%).

2-N-*Phenylpicrylaminopyridine*, prepared from 2 : 4 : 6-trinitrodiphenyl ether (3·0 g.; Willgerodt, *Ber.*, 1879, **12**, 1277) and 2-aminopyridine (950 mg.), formed red prisms (100 mg.), m. p. 229—231°, from acetic acid (Found: C, 53·7; H, 3·2; N. 18·4. $C_{17}H_{11}O_6N_5$ requires C, 53·5; H, 2·9; N, 18·4%).

1 : 2 : 3 : 4-*Tetrahydro*-8-*picrylaminocarbazole*, prepared by heating 8-amino-1 : 2 : 3 : 4-tetrahydrocarbazole (9·3 g.; Edwards and Plant, *J.*, 1923, 2398), fused sodium acetate (8·0 g.), and anhydrous benzene (100 ml.) for 1 hour, then cooling the solution and adding ligroin (200 ml.), formed red prismatic needles (13.5 g.), m. p. 248° (decomp.), from toluene (1 l.) (Found: C, 54·8; H, 4·1; N, 17·4. $C_{18}H_{15}O_6N_5$ requires C, 54·4; H, 3·8; N, 17·6%).

Attempts at ring closure included treatment with quinoline under reflux, dimethylaniline at 200°, and hot alcoholic potassium hydroxide, and sublimation at 205—210°/0·03 mm. Phenol–nitrobenzene at 200° (0·5 hour) gave a brown amorphous *substance* (200 mg.), m. p. >310° (Found : C, 62·5; H, 3·7; N, 15·0. $C_{18}H_{14}O_4N_4$ requires C, 61·7; H, 4·0; N, 16·0%).

1-*Picrylaminocarbazole* formed crimson prisms (80%) (from acetic acid), m. p. 274—275° (decomp.) (Found : C, 55·2; H. 2·9; N, 18·1. $C_{18}H_{11}O_6N_5$ requires C, 55·0; H, 2·8; N, 17·8%). When phenol–nitrobenzene was used to effect ring closure, a red-brown amorphous *substance* was obtained, having m. p. >300° (Found : C, 64·1; H, 2·7; N, 15·3. $C_{18}H_{10}O_4N_4$ requires C, 62·4; H, 2·9; N, 16·2%).

1-*Methyl*-4-*nitro*-5-*o*-*hydroxyanilinoglyoxaline* (IV).—5-Chloro-1-methyl-4-nitroglyoxaline (8·0 g.), *o*-aminophenol (5·0 g.), fused sodium acetate (5·0 g.), potassium iodide (1 crystal), and ethanol (100 ml.) were heated under reflux for 24 hours. After cooling to 5° the solids were collected and crystallised from ethanol to give 1-*methyl*-4-*nitro*-5-*o*-*hydroxyanilinoglyoxaline*, yellow needles (6·0 g.), m. p. 222—224° (decomp.) (Found : C, 51·1; H, 4·4; N, 24·1. $C_{10}H_{10}O_3N_4$ requires C, 51·3; H, 4·3; N, 23·9%). The compound dissolved in sodium hydroxide to give a red solution.

Ring closure was effected by heating the foregoing compound (5·0 g.) in ethanol (400 ml.) and diethylamine (40 ml.) in a sealed tube at 120° for 16 hours. Blue needles (1·1 g.) were collected. The *substance* was recrystallised from amyl alcohol (1·5 l.), to give blue needles, m. p. >310° (Found : C, 63·8; H. 4·1; 3·8; N, 21·9. $C_{10}H_8ON_3$ requires C, 64·5; H, 4·3; N, 22·5. $C_{10}H_7ON_3$ requires C, 64·8; H, 3·8; N, 22·7%). The compound is slightly soluble in dioxan and in concentrated sulphuric acid, to give intense blue solutions. The absorption spectrum in sulphuric acid and dioxan were kindly determined for us by Dr. H. Campbell (see table for the approximate figures). Considerable changes occurred when the sulphuric acid solution was kept, with marked intensification of the spectrum.

Conc. H_2SO_4 solution [4×10^{-3} g. per litre]		Dioxan solution [concn. unknown]
$\lambda_{max.}$	$E^{1\%}_{1\,cm.}$	$\lambda_{max.}$
260	300	—
380	300	320
480	230	[480] *
510	420	500
550	480	540

* Submerged maximum.

Reduction. The blue compound (4·0 g.) in concentrated sulphuric acid (200 ml.) was treated at 10—20° with zinc dust (4·0 g.). As the reduction proceeded the deep violet colour faded and, after an hour, the pale red suspension was filtered and the filtrate added to oxygen-free water (5 l.). The pink solution was treated with barium hydroxide solution at 15—30° in an atmosphere of hydrogen to precipitate sulphate, and the pink filtrate concentrated *in vacuo* to 100 ml. in a stream of hydrogen. The pink *substance* thus obtained had m. p. 250—255° (Found : N, 22·1; 22·0. $C_{10}H_7ON_3$ requires N, 22·7%), but could not be recrystallised owing to extremely rapid oxidation to the blue compound.

One of us (S. S. B.) thanks the Directors of May and Baker Ltd. for research facilities.

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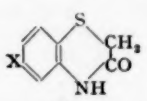
142. *Preparation of* 2 : 3-*Dihydro*-3-*ketobenzo*-1 : 4-*thiazine Derivatives as Possible Anthelmintics.*

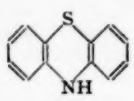
By ALEXANDER MACKIE and JOHN RAEBURN.

Derivatives of 2 : 3-dihydro-3-ketobenzo-1 : 4-thiazine have been prepared, mainly from the diazonium compound from the 6-amino-derivative, for test against parasitic worms *in vitro*. Nearly all the derivatives produced a paralysant effect on liver fluke (*Fasciola hepatica*).

2 : 3-DIHYDRO-3-KETOBENZO-1 : 4-THIAZINE (I; X = H) and some derivatives thereof have been prepared, as it was considered that they might show some anthelmintic properties : these compounds have some features of phenothiazine (II), extensively used in veterinary practice, and of filicic acid (III), an important constituent of *Filix mas*.

Few derivatives of 2 : 3-dihydro-3-ketobenzo-1 : 4-thiazine have been synthesised. Friedlaender and Chwala (*Monatsh.*, 1907, **28**, 252) showed that when (*o*-nitroarylthio)-acetic acids were reduced, the resulting aminoarylthio-acids split off a molecule of water with extraordinary ease, with ring closure to benzo-1 : 4-thiazine derivatives.


(I)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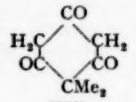
(III)

2 : 3-Dihydro-3-ketobenzo-1 : 4-thiazine and its 6 : 7-dimethoxy-derivative were obtained by reduction of the appropriate (nitrophenylthio)acetic acids (Claasz, *Ber.*, 1912, **45**, 751; Baldick and Lions, *J. Roy. Soc. N.S.W.*, 1937—38, **71**, 113).

Most of the derivatives described in this investigation were prepared by way of the diazonium compound from 6-amino-2 : 3-dihydro-3-ketobenzo-1 : 4-thiazine (I; X = NH_2), obtained by reduction of (2 : 4-dinitrophenylthio)acetic acid (Friedlaender and Chwala, *loc. cit.*, p. 276). Many of the yields were small, principally owing to the difficulty in obtaining the compounds analytically pure. The amino-group was replaced successfully by F, Cl, I, CNS, N_3, NO_2, NO, SH, H_2AsO_3, H_2SbO_3, and HgCl, and decomposition of the diazonium compound by copper bronze afforded the bis-derivative. The 6-bromo-compound was not obtained by Sandmeyer reaction, but by decomposition of the perbromide. The 6-hydroxy-derivative could not be prepared from the diazonium compound. A deep red colour was obtained, which indicated self-coupling. The 6 : 7-dihydroxy-compound was, however, easily prepared from the 6 : 7-dimethoxy-derivative. The amino-group could not be replaced by the cyanogen group by Sandmeyer reaction, and attempts to produce a Grignard reagent from the iodo-derivative were fruitless.

The derivatives described herein have been tested against and had practically no effect on the round worm, *Ascaris lumbricoides*, but nearly all showed a paralysant effect on liver fluke (*Fasciola hepatica*) *in vitro*. Full details will be published elsewhere. The 6-chloro-derivative was the most effective.

Experimental

M. p.s are uncorrected.

6-*Amino*-2 : 3-*dihydro*-3-*ketobenzo*-1 : 4-*thiazine*.—Reduction of (2 : 4-dinitrophenylthio)-acetic acid, m. p. 172° (Friedlaender and Chwala, *loc. cit.*, record m. p. 167—168°), with tin and hydrochloric acid afforded the 6-amino-compound. Contrary to the findings of Friedlaender and Chwala (*loc. cit.*) who preferred using iron and acetic acid, the former reagents proved superior. Reduction in alcohol with iron and hydrochloric acid (West's method, *J.*, 1925, **127**, 494) was unsatisfactory.

The hydrochloride decomposed at 272—274°, and the acetyl derivative had m. p. 257°. Friedlaender and Chwala (*loc. cit.*) give m. p. 257° for the latter compound, but record few experimental details. Satisfactory yields were only obtained after 16 hours' refluxing with acetic anhydride.

The amino-compound was easily diazotised below 10°, and for each of the derivatives prepared by way of the diazo-reaction, 4·5 g. of amino-derivative were used.

6-*Fluoro*-2 : 3-*dihydro*-3-*ketobenzo*-1 : 4-*thiazine*.—Fluoroboric acid (40% solution; 20 c.c.) was added to the cold diazonium solution. The mixture was stirred for 2 hours, a pale yellow precipitate of the diazonium fluoroborate separating, which was filtered off, washed with water, ethanol, and ether, and finally dried (6 g.). The diazonium fluoroborate was decomposed at 135° (vapour from boiling xylene) and the 6-*fluoro*-2 : 3-*dihydro*-3-*ketobenzo*-1 : 4-*thiazine* in the residue was extracted with boiling absolute ethanol. An orange-brown impurity, which separated when the alcoholic extract cooled, was removed, and the fluoro-compound in the filtrate was isolated and recrystallised from aqueous ethanol in pale yellow platelets (1 g.), m. p. 184° (Found: C, 52·4; H, 3·2; N, 7·7. C_8H_6ONFS requires C, 52·5; H, 3·3; N, 7·7%).

6-*Chloro*-2 : 3-*dihydro*-3-*ketobenzo*-1 : 4-*thiazine*.—The amino-group was replaced by chlorine in a Sandmeyer reaction (Friedlaender and Chwala, *loc. cit.*).

6-*Bromo*-2 : 3-*dihydro*-3-*ketobenzo*-1 : 4-*thiazine*.—Decomposition of the perbromide at 155° afforded a compound, m. p. 220° (Found : N, 5·0. Calc. for C_8H_6ONBrS : N, 5·7%). A purer product could not be obtained.

6-*Iodo*-2 : 3-*dihydro*-3-*ketobenzo*-1 : 4-*thiazine*.—A saturated aqueous solution of potassium iodide (8 g.) was added to the cold diazonium solution. The reaction mixture was stirred during 5 hours, then refluxed for 1 hour with ethanol (200 c.c.), and the solution filtered hot. The crystals obtained on cooling of the filtrate were recrystallised from aqueous ethanol, giving the 6-*iodo*-compound as feathery orange needles (3·5 g.), m. p. 208—210° (Found : I, 43·5; N, 5·1. C_8H_6ONIS requires I, 43·6; N, 4·8%).

2 : 3-*Dihydro*-3-*keto*-6-*thiocyanatobenzo*-1 : 4-*thiazine*.—Potassium thiocyanate (4 g.) in aqueous solution, followed by a paste containing cuprous thiocyanate, was added to the cold diazonium solution. The paste was prepared by adding potassium thiocyanate (4 g.) in aqueous solution to a solution containing copper sulphate (8 g.) and ferrous sulphate (16 g.), filtering, and making the residue into a paste with water. The mixture was vigorously agitated for 9 hours, then the reaction product was refluxed with ethanol (200 c.c.) for 1·5 hours. After filtration, the filtrate deposited orange crystals which were recrystallised from aqueous ethanol. 2 : 3-*Dihydro*-3-*keto*-6-*thiocyanatobenzo*-1 : 4-*thiazine* was obtained as pale yellow needles (3 g.), m. p. 180° (Found : C, 48·4; H, 3·1; N, 12·3. $C_9H_6ON_2S_2$ requires C, 48·6; H, 2·7; N, 12·6%).

6-*Azido*-2 : 3-*dihydro*-3-*ketobenzo*-1 : 4-*thiazine*.—Sodium azide (2 g.) in aqueous solution was slowly added to the cold diazonium solution. Nitrogen was evolved and a white precipitate formed. The mixture was stirred below 10° for 5 hours, and then allowed to attain room temperature. The precipitate was filtered off, washed, and recrystallised from aqueous ethanol. 6-*Azido*-2 : 3-*dihydro*-3-*ketobenzo*-1 : 4-*thiazine* was obtained as pale yellow feathery needles (5 g.), becoming yellowish-brown with slight decomposition on exposure to light, m. p. 176° (decomp.) (Found : N, 27·0. $C_8H_6ON_4S$ requires N, 27·2%).

2 : 3-*Dihydro*-3-*keto*-6-*nitrobenzo*-1 : 4-*thiazine* (cf. Hodgson and Marsden, *J.*, 1944, 22).—The diazonium solution was neutralised with calcium carbonate and filtered. Finely powdered sodium cobaltinitrite (11 g.) was then added to the filtrate and the diazonium cobaltinitrite which separated was filtered off and dried. The diazonium cobaltinitrite (10 g.) was added in portions at room temperature to an aqueous solution containing sodium nitrite (10 g.) and copper sulphate (10 g.), in which cuprous oxide (4 g.) was suspended. After evolution of nitrogen was complete, the product was filtered off. The greenish residue was recrystallised from ethanol, giving the 6-*nitro-thiazine* as golden-brown feathery needles (1 g.), m. p. 243—244° (Found : N, 13·6. $C_8H_6O_3N_2S$ requires N, 13·3%).

2 : 3-*Dihydro*-3-*keto*-6-*nitrosobenzo*-1 : 4-*thiazine*.—The diazonium solution was run into a saturated solution of potassium permanganate (70 c.c.) below 10° and the mixture rendered alkaline with aqueous potassium hydroxide. After 3 hours' stirring, the mixture was extracted with ether, and on removal of the ether the residue was recrystallised from aqueous ethanol, giving 2 : 3-*dihydro*-3-*keto*-6-*nitrosobenzo*-1 : 4-*thiazine* as pale yellow platelets (0·2 g.), m. p. 134° (Found : N, 14·7. $C_8H_6O_2N_2S$ requires N, 14·4%).

2 : 3-*Dihydro*-3-*keto*-6-*mercaptobenzo*-1 : 4-*thiazine*.—Aqueous potassium xanthate (4 g.) was added to the cold diazonium solution. After 2 hours, a bright yellow precipitate was obtained, the temperature of the reaction mixture was gradually raised, and decomposition completed on the water-bath (1·5 hours). The yellow precipitate was filtered off and refluxed with alcoholic potassium hydroxide until hydrolysis of the ethyl thiocarbonic acid derivative was complete (1 hour). After removal of the ethanol, the residue was dissolved in water, and the solution filtered and acidified with dilute sulphuric acid. The yellow precipitate was filtered off and recrystallised from aqueous ethanol; the *mercapto-thiazine* was obtained as pale yellow needles (3 g.), m. p. 174° (Found : C, 48·9; H, 3·2; N, 7·4. $C_8H_7ONS_2$ requires C, 48·7; H, 3·6; N, 7·1%).

2 : 3-*Dihydro*-3-*ketobenzo*-1 : 4-*thiazine*-6-*arsonic Acid*.—A solution of sodium arsenite (25 c.c.; 20%) was added to the cold diazonium solution, and the mixture rendered alkaline with aqueous sodium hydroxide. After being stirred (3—4 hours), the solution was filtered, the filtrate acidified and boiled with animal charcoal, and the purified filtrate made strongly acid. Brownish crystals were obtained on cooling and were recrystallised from hot water. The *arsonic acid* formed pale yellow plates (0·5 g.), decomp. >300° (Found : C, 33·3; H, 2·7; N, 5·0. $C_8H_8O_4NSAs$ requires C, 33·2; H, 2·8; N, 4·8%).

2 : 3-*Dihydro*-3-*ketobenzo*-1 : 4-*thiazine*-6-*stibonic Acid*.—A solution of antimony trioxide (8 g.) in concentrated hydrochloric acid, added to the ice-cold diazonium solution, gave the *stibonic acid*. This was purified by dissolution in aqueous sodium carbonate and reprecipit-

ation with acid, and then formed a reddish-brown amorphous powder (1 g.), decomp. >270° (Found: C, 28·8; H, 2·5; N, 3·9. $C_8H_8O_4NSSb$ requires C, 28·6; H, 2·4; N, 4·2%).

6-Chloromercuri-2 : 3-dihydro-3-ketobenzo-1 : 4-thiazine.—The diazonium solution was added to a solution of mercuric chloride (7 g.) in concentrated hydrochloric acid (7 c.c.) mixed with ice (7 g.). After 2 hours' stirring at 0°, the diazonium mercurichloride was filtered off, dried, and decomposed with copper bronze (6 g.) in presence of acetone (80 c.c.) at 0° (3 hours). The temperature was then raised slowly and decomposition completed on the water-bath (1 hour). On cooling, the product was filtered off and recrystallised from nitrobenzene. The *chloromercuri-thiazine* was obtained as pale yellow needles (1 g.), m. p. 263—264° (decomp.) (Found: C, 24·3; H, 1·2; N, 3·4. $C_8H_6ONClSHg$ requires C, 24·0; H, 1·5; N, 3·5%).

Bis-(2 : 3-dihydro-3-ketobenzo-1 : 4-thiazin-6-yl).—An aqueous alcoholic solution of the diazonium compound was decomposed with copper bronze (5 g.) introduced slowly, the temperature being kept below 30°. After 1 hour, the temperature was raised gradually to 75°, whereupon a vigorous reaction took place, and the resulting reddish-brown precipitate was filtered off. Excess copper was removed, and the residue was purified by refluxing it with absolute ethanol. The *dithiazinyl* was obtained as a brown amorphous powder (3·5 g.), m. p. >330° (Found: N, 8·3. $C_{16}H_{12}O_2N_2S_2$ requires N, 8·5%).

2 : 3-Dihydro-6 : 7-dihydroxy-3-ketobenzo-1 : 4-thiazine.—2 : 3-Dihydro-3-keto-6 : 7-dimethoxybenzo-1 : 4-thiazine (5 g.) (Baldick and Lions, *loc. cit.*) was refluxed with a large excess of constant-boiling hydriodic acid for 2 hours. On removal of methyl iodide and addition of a large volume of water, brown crystals separated, which were purified by recrystallisation from distilled water out of contact of air. The *dihydroxy-thiazine* crystallised as pale pink rectangular plates (1 g.), decomp. >240°, becoming deep pink on exposure to air. A purple colour, changing quickly to sky blue, developed with aqueous sodium hydroxide, but no colour with ferric chloride (Found: C, 48·8; H, 3·2; N, 7·0. $C_8H_7O_3NS$ requires C, 48·7; H, 3·6; N, 7·1%).

The authors' thanks are due to Principal Nisbet for his interest in this work and to Dr. J. W. Minnis and Mr. A. T. Macdonald for the microchemical analyses. Financial support from the Agricultural Research Council is gratefully acknowledged.

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143. *Dismutation Reactions of Di-*p*-methoxyphenylmethanol.*

By M. P. BALFE, J. KENYON, and E. M. THAIN.

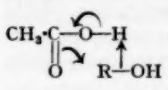
Di-*p*-methoxyphenylmethanol with 0·5 mol. of weak acids yields bisdi-*p*-methoxyphenylmethyl ether; with stronger acids it yields di-*p*-methoxyphenyl ketone and di-*p*-methoxyphenylmethane. The bis-ether and di-*p*-methoxyphenylmethyl ethyl ether, in ethanol–hydrochloric acid, yield di-*p*-methoxyphenylmethane and acetaldehyde; the ethyl ether, in propanol–hydrochloric acid, yields the methane and *n*-propaldehyde. It is suggested that the conjugate acids of di-*p*-methoxyphenylmethyl ethers are intermediates in these dismutations.

WE have already presented evidence (*J.*, 1951, 386) to indicate that di-*p*-methoxyphenylmethanol has very little tendency to react by virtue of its hydroxylic hydrogen atom but readily undergoes reactions which appear to imply carbonium-ion formation. This unusual behaviour of a secondary alcohol has been further examined.

*Action of Acids on Di-*p*-methoxyphenylmethanol.*—(i) Acetic acid in excess either at room temperature or at 100° within a few hours converts the alcohol quantitatively into its acetate. On the other hand, when a half-molecular proportion of acid is heated with the alcohol at 100°, the product is bisdi-*p*-methoxyphenylmethyl ether.

(ii) Formic acid readily dissolves the alcohol, giving a deep red solution from which only polymerised material can be isolated. On the other hand, a mixture of the acid (0·5 mol.) and the alcohol after 4 days at room temperature yielded the bis-ether (60%). It seems probable that the deep colour of the formic acid solution is due to the formation of carbonium ions, a view to which support is given by the ready reaction of this solution with

urea and with sodium toluene-*p*-sulphinate to give respectively the disubstituted urea and di-*p*-methoxyphenylmethyl *p*-tolyl sulphone. Neither of these condensations takes place in acetic acid solution but both occur readily when a drop of sulphuric acid has been added, the solution becoming red. This suggests that di-*p*-methoxyphenylmethanol does not give rise to carbonium ions in acetic acid solution in the absence of strong acid and the ready formation of its acetate is therefore not likely to be due to an alkyl–oxygen fission reaction of the unimolecular type. The carbinol is also not prone to react by alkoxyl–hydrogen fission (*loc. cit.*). Possibly its esterification is bimolecular with alkyl-oxygen fission. Xanthhydrol would appear to undergo alkyl–oxygen fission even more readily than does di-*p*-methoxyphenylmethanol since it reacts with amides in acetic acid to yield the corresponding xanthhydryl derivatives (Fosse, *Compt. rend.*, 1907, **145**, 813); it reacts also in this solvent with sodium toluene-*p*-sulphinate to give *p*-tolyl xanthhydryl sulphone. The tolyl sulphones of di-*p*-methoxyphenylmethanol and xanthhydrol undergo reactions which indicate that the C–S bond breaks. Whilst in general they are stable to acids, with alcoholic potassium hydroxide they yield ethyl ethers, presumably by combination of a carbonium ion with ethoxyl:



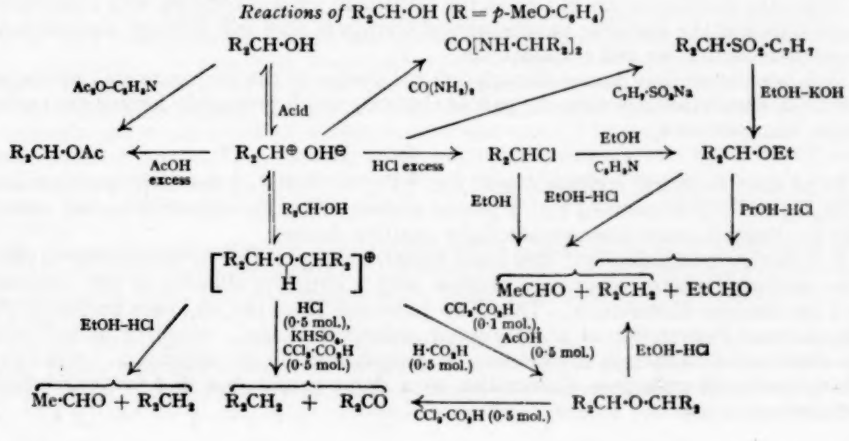
$$R\dot{-}SO_2{\cdot}C_7H_7 + H\dot{-}OEt \longrightarrow R{\cdot}OEt + C_7H_7{\cdot}SO_2H.$$

(iii) Trichloroacetic acid in small proportions converts di-*p*-methoxyphenylmethanol into its bis-ether but in higher concentrations effects its dismutation into *pp'*-dimethoxybenzophenone and di-*p*-methoxyphenylmethane, a reaction analogous to that undergone by xanthhydrol (Kny-Jones and Ward, *J.*, 1930, 535).

Dismutation of Di-p-methoxyphenylmethanol.—The dismutation of both di-*p*-methoxyphenylmethanol and xanthhydrol is hindered by the use of dioxan as solvent—as is also ether formation—probably owing to solvent–oxonium salt formation. Other strong acids also cause dismutation, *e.g.*, potassium hydrogen sulphate and hydrochloric acid (0·5 mol.).

Kny-Jones and Ward (*loc. cit.*) observed that xanthhydryl chloride reacts with ethyl alcohol, giving xanthen, and although they did not isolate acetaldehyde they found that the reaction solution gave a positive result with Schiff's reagent.

Di-*p*-methoxyphenylmethyl chloride reacts similarly with ethyl alcohol to give di-*p*-methoxyphenylmethane and acetaldehyde (isolated in 75% yield as its 2 : 4-dinitrophenylhydrazone); when pyridine is present di-*p*-methoxyphenylmethyl ethyl ether is produced. This ether also undergoes dismutation in acid solution yielding, when ethyl alcohol is the solvent, the substituted methane and acetaldehyde; when *n*-propyl alcohol is the solvent, propaldehyde and not acetaldehyde is isolated. Similarly bisdi-*p*-methoxyphenylmethyl ether undergoes dismutation in alcoholic solution containing hydrochloric acid, yielding di-*p*-methoxyphenylmethane and acetaldehyde.

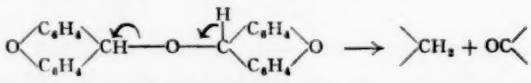


Thermal dismutation of diphenylmethyl derivatives to the corresponding benzophenone and diphenylmethane derivatives has been observed by Nef (*Annalen*, 1897, **298**, 202) and Goldthwaite (*Amer. Chem. J.*, 1905, **33**, 92). Since small amounts of the corresponding *s*-tetraphenylethane derivatives, formed by dimerisation, were also isolated it seems probable that these reactions proceed by a free-radical mechanism.

However, in acid-catalysed dismutation reactions a free-radical mechanism is unlikely because of the polar nature of the solution, and also because of the contrasted behaviour of di-*p*-methoxyphenylmethyl ethyl ether, which by acid-catalysed dismutation yields di-*p*-methoxyphenylmethane but by thermal dismutation yields this compound in only small amounts, the main product being the corresponding ketone, by a reaction more likely to proceed by a free-radical mechanism.

Furthermore no dimerisation products were isolated in the acid-catalysed reactions enumerated above.

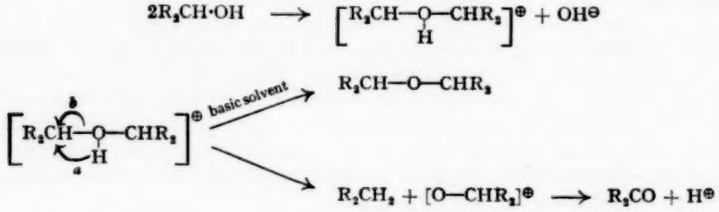
Kny-Jones and Ward (*loc. cit.*) considered that the dismutation of xanthhydrol occurred through the intermediate formation of its ether :



they noted, however, that dixanthhydryl ether undergoes dismutation less readily than does xanthhydrol itself.

A parallel behaviour has not been observed in the relative tendencies of di-*p*-methoxyphenylmethanol and its bis-ether to undergo dismutation by acid catalysis.

Accordingly, it appears more probable that the essential step in the process is the formation, not of an ether, but rather of its precursor, the conjugate acid, by carbonium-ion addition to an alcohol molecule. This conjugate acid may, by proton expulsion, yield the ether—a process likely to be favoured by the presence of pyridine or dioxan—or, alternatively, undergo dismutation.



When the reaction occurs in alcohol the carbonium ion will combine with a molecule of the solvent and the resulting unsymmetrical conjugate acid will undergo dismutation to the methane derivative and acetaldehyde.

It is postulated that during dismutation the proton of the conjugate acid moves over (process *a*) simultaneously with the pair of electrons which previously formed the carbon–oxygen link (process *b*).

In an unsymmetrical conjugate acid, *e.g.*, $\left[\begin{matrix}H\\|\\Et—O—CHR_2\end{matrix}\right]^{\oplus}$, the CHR_2 part is reduced to CH_2R_2, and if it is assumed that a proton migrates then the secondary carbon atom, in order to attract it, must possess some slight negative charge.

It is further postulated that this small negative charge is due to the mesomeric effects of the methoxyl groups, since only alcohols with a structure allowing of this mesomeric effect can undergo dismutation. Thus Kny-Jones and Ward (*loc. cit.*) were unable to effect acid-catalysed dismutation of unsubstituted diphenylmethanol. Michler's hydrol undergoes dismutation, although the reaction is complicated by tar formation. *p*-Methoxydiphenylmethanol undergoes dismutation to a slight extent, but di-*p*-*tert.*-butylphenylmethanol not at all.

Experimental

Action of Acetic Acid on Di-p-methoxyphenylmethanol.—(a) *Acetic acid in excess.* A solution of the alcohol (0·5 g.) in glacial acetic acid (2 c.c.) was kept at room temperature for 12 hours. Dilution with water precipitated an oil which rapidly solidified (0·5 g.), having m. p. 68—73°; crystallisation from ether–light petroleum (3 c.c.; 1 : 1) yielded di-*p*-methoxyphenylmethyl acetate as needles, m. p. 78—80° undepressed on admixture with a specimen prepared by the action of acetic anhydride as described by Schnackenberg and Scholl (*Ber.*, 1903, **36**, 655). The same result was obtained when the reaction mixture was kept at 100° for 2 hours.

(b) 0·5 *Mol. of acetic acid.* A mixture of the alcohol (0·5 g.) and glacial acetic acid (0·1 g., 0·5 mol.) was kept at 100° for 2 hours and then diluted with water. The precipitated material, after two crystallisations from ethanol, yielded *bisdi-*p*-methoxyphenylmethyl ether* (0·25 g.), needles, m. p. 81—82° (Found: C, 76·2; H, 6·5. $C_{30}H_{30}O_5$ requires C, 76·6; H, 6·4%).

Attempted Preparation of Xanthhydryl Acetate.—Acetic anhydride (0·52 g., 1 mol.) was added to a solution of xanthhydrol (1·0 g.) in dry pyridine (1 c.c.). After 2 days at room temperature the mixture was diluted with crushed ice and made just acid to Congo-red. The dried precipitate (1·0 g.), m. p. 175—185° (after crystallisation from benzene), yielded dixanthhydryl ether, m. p. 212—214°, undepressed on admixture with an authentic specimen.

Action of Formic Acid on Di-p-methoxyphenylmethanol.—(a) *Formic acid in excess.* The alcohol (0·5 g.) dissolved readily in cold formic acid (2 c.c. of 99%) giving a deep red solution which after 30 minutes had become cloudy. After 4 days the separated solid was removed and dried (0·35 g.). Crystallisation from ethanol yielded a pale yellow powder which sintered at 60—80° [*M* (Rast), 900].

(b) 0·5 *Mol. of formic acid.* After 4 days at room temperature there was isolated bisdi-*p*-methoxyphenylmethyl ether, m. p. and mixed m. p. 76—78°, in 60% yield.

*Bisdi-*p*-methoxyphenylmethylurea.*—(*a*) A solution of the alcohol (0·2 g.) in formic acid (1 c.c.) was added to urea (0·06 g.) in formic acid (1 c.c.). The brilliant red colour of the alcohol solution faded at once, and a white solid began to separate. After 20 minutes water was added and the solid material (0·2 g.), m. p. 252—254°, crystallised from ethanol or acetone. *Bisdi-*p*-methoxyphenylmethylurea* forms fine needles, m. p. 258—259° (Found: C, 72·1: H, 6·2: N, 5·6. $C_{31}H_{32}O_5N_2$ requires C, 72·7: H, 6·2: N, 5·5%).

(*b*) In acetic acid only a trace of the urea was formed, the main product being di-*p*-methoxyphenylmethyl acetate (mixed m. p.). When, however, the acid contained a drop of concentrated sulphuric acid the substituted urea was readily obtained [mixed m. p. with product from (*a*)].

*Di-*p*-methoxyphenylmethyl* p*-Tolyl Sulphone.*—(*a*) Di-*p*-methoxyphenylmethyl chloride (1·0 g.), prepared by the action of cold concentrated hydrochloric acid on the alcohol, was added to a solution of sodium toluene-*p*-sulphinate (1·0 g., 1·5 mols.) in aqueous acetone. After 12 hours at room temperature the yellow solution was diluted with water; the precipitated material, after crystallisation from ether–light petroleum, yielded the sulphone (0·9 g.), m. p. 105—106° alone and when mixed with an authentic specimen (Balfe, Kenyon, and Thain, *J.*, 1951, 386).

(*b*) A solution of di-*p*-methoxyphenylmethanol (1·0 g.) in acetic acid (2 c.c.) containing sulphuric acid (1 drop) was mixed with a solution of sodium toluene-*p*-sulphinate (0·73 g.) in acetic acid (4 c.c.). The brilliant red colour of the alcoholic solution disappeared immediately and after an hour the opalescent solution was diluted and the precipitated sulphone crystallised (m. p. 105—106°). Di-*p*-methoxyphenylmethyl *p*-tolyl sulphone is unaffected by being heated at 100° for 3 hours with glacial acetic acid, or 1 : 1 concentrated hydrochloric acid–dioxan.

*Di-*p*-methoxyphenylmethyl Ethyl Ether.*—(*a*) Di-*p*-methoxyphenylmethyl chloride (2·4 g.) was added to dry pyridine (1·2 g.), a solid being formed with the liberation of heat; to this was added ethanol (5 c.c.), and the resulting brown solution was heated under reflux for 4·5 hours. After working up in the usual way the *ethyl ether* (2·1 g., 85%) was obtained, having b. p. 153°/0·5 mm., 217—220°/14 mm., n_D^{19} 1·5594 (Found: C, 75·0: H, 7·4. $C_{17}H_{20}O_3$ requires C, 75·0: H, 7·35%).

(*b*) Di-*p*-methoxyphenylmethyl *p*-tolyl sulphone (0·3 g.) was heated for 10 hours under reflux with ethanolic potassium hydroxide (5 c.c.; N; 80% alcohol). After evaporation of the solvent and working up there was obtained the ethyl ether, b. p. 145—150° (bath-temp.)/0·3 mm., n_D^{19} 1·5610.

p-*Tolyl Xanthhydryl Sulphone.*—Xanthhydrol (2·0 g.) and sodium toluene-*p*-sulphinate (1·8 g., 1 mol.) were each dissolved in warm glacial acetic acid (5 c.c.), and the solutions mixed. Crystals began to separate at once and after 2 hours were removed and washed with alcohol: they (2·4 g.) had m. p. 210—215°. Crystallisation from ethanol yielded p-*tolyl xanthhydryl*

sulphone, needles, m. p. 215—216° (Found : S, 9·7. $C_{20}H_{16}O_3S$ requires S, 9·55%). This sulphone was unchanged after 3 hours' heating at 100° with acetic or formic acid.

Action of Hydrochloric Acid (0·5 Mol.) on Di-p-methoxyphenylmethanol.—Hydrochloric acid (0·3 c.c. ; 6N ; 0·5 mol.) was added to a solution of the alcohol (1·0 g.) in acetone (5 c.c.). After evaporation at room temperature a pale pink oil remained which crystallised from ether–light petroleum (15 c.c. ; 1 : 1) yielding di-*p*-methoxyphenyl ketone (0·3 g.), m. p. and mixed m. p. 142—143°. The filtrate on evaporation left an oil which crystallised on storage (0·1 g.) ; after crystallisation from light petroleum this had m. p. 46—48° alone or when mixed with authentic di-*p*-methoxyphenylmethane (see below).

Action of Potassium Hydrogen Sulphate on Di-p-methoxyphenylmethanol.—A mixture of finely ground potassium hydrogen sulphate (0·5 g.) and the alcohol (1·0 g.) was heated at 100° for 3 hours. The water-insoluble portion of the reaction product was separated by fractional crystallisation into di-*p*-methoxyphenyl ketone (0·5 g.) and di-*p*-methoxyphenylmethane (0·2 g.), identified by m. p. and mixed m. p. in each case.

Reaction between Di-p-methoxyphenylmethyl Chloride and Ethyl Alcohol.—A solution of the chloride (0·5 g.) in ethanol (2 c.c. ; 96%) was heated under reflux for 6 hours, a slow stream of carbon dioxide passing through the reaction flask and into two wash-bottles containing 2 : 4-dinitrophenylhydrazine in hydrochloric acid (0·2% ; 2N). Acetaldehyde 2 : 4-dinitrophenylhydrazone (0·32 g. ; 75%), m. p. 160—161°, was precipitated ; after crystallisation from ethanol it had m. p. 165—167° alone and mixed with an authentic specimen.

Ethanol was removed from the non-volatile residue at room temperature, and the residual oil dissolved in ether, washed, and dried (K_2CO_3). The resulting di-*p*-methoxyphenylmethane (0·35 g., 80%) had b. p. 149—151°/0·4 mm., m. p. 49—51° undepressed when mixed with the specimen prepared as described above (Städel and Beck, *Annalen*, 1878, **194**, 323, record m. p. 48—49°).

Formation of Ethyl Xanthhydryl Ether from the Sulphone.—*p*-Tolyl xanthhydryl sulphone (1·0 g.) was heated under reflux with ethanolic potassium hydroxide (20 c.c. ; N, 80% alcohol) for 4 hours. The alcohol was evaporated, the residue diluted with water, and the precipitated oil extracted with light petroleum. The insoluble solid had m. p. 120—125° : it (0·1 g.) was separated by crystallisation from ether–light petroleum into dixanthhydryl ether (0·02 g.), m. p. and mixed m. p. 203—205°, and xanthhydrol (0·06 g.), m. p. and mixed m. p. 122—123°. The light petroleum extract yielded *ethyl xanthhydryl ether* (0·5 g., 74%) as an oil which slowly crystallised and then had m. p. 50—60°. Two sublimations at 0·1 mm. yielded the pure material as prisms, m. p. 53—54° (Found : C, 79·7 : H, 6·1. $C_{15}H_{14}O_2$ requires C, 79·7 : H, 6·2%).

Dismutation of Di-p-methoxyphenylmethanol and of Bisdi-p-methoxyphenylmethyl Ether by Trichloroacetic Acid in Benzene or Dioxan.—The alcohol (or ether) (1·0 g.) was heated at 40° in benzene or dioxan (1 c.c.) containing varying amounts of trichloroacetic acid, air above the reaction mixture being displaced by nitrogen. Both pure dioxan and a specimen containing peroxides were used but no difference was noted between the reaction products. After the heating, ether (5 c.c.) was added and the solution was washed with alkali and dried (Na_2SO_4). The residue after evaporation of the solvent was triturated with light petroleum (3 × 2 c.c.) in which di-*p*-methoxyphenylmethane is readily soluble : the combined petroleum extracts on evaporation yielded crystalline di-*p*-methoxyphenylmethane. The undissolved residue was triturated with cold ether–light petroleum (10 c.c. ; 1 : 4) in which di-*p*-methoxyphenyl ketone is practically insoluble and can be removed therefrom by filtration. The ether–light petroleum extract was evaporated and the residue crystallised—from ether–light petroleum if consisting mainly of di-*p*-methoxyphenylmethanol, or from ethanol if consisting mainly of bisdi-*p*-methoxyphenylmethyl ether. Results are in the following Table.

Di-p-*methoxyphenylmethanol* (2 hours)

$CCl_3{\cdot}CO_2H$ (g.)	Solvent	Products isolated
0·07 (0·1 mol.)	Benzene	Ether 80%
0·07	Dioxan	Ether 40, unchanged alcohol 50%
0·35 (0·5 mol.)	Benzene	Ether 25, ketone 10, methane 5%
0·35	Dioxan	Ether 84%
0·35	None	Ketone 43, methane 32%.

Bisdi-p-*methoxyphenylmethyl ether* (6 *hours*).

0·35	Benzene	Ether 35, ketone 14, methane 3%
0·35	Dioxan	Ether 84%

Decomposition of Di-p-methoxyphenylmethyl Ethyl Ether with Acids.—(*a*) A solution of the ethyl ether (1·0 g.) and trichloroacetic acid (0·35 g.) in benzene (1 c.c.) was heated under reflux, a stream of carbon dioxide carrying any volatile products into 2 : 4-dinitrophenylhydrazine solution (also in other experiments recorded below). No volatile aldehydes or ketones were formed; di-*p*-methoxyphenyl ketone (0·11 g.), m. p. 139—141°, and di-*p*-methoxyphenylmethane (0·15 g.), b.p. 148°/0·3 mm., m. p. and mixed m. p. 48—50°, were isolated but the main product was an intractable tar.

(*b*) A solution of the ethyl ether (0·5 g.) in aldehyde-free ethanol (2 c.c.) containing hydrochloric acid (0·18 c.c., 1 mol.) was heated under reflux for 8 hours. Acetaldehyde 2 : 4-dinitrophenylhydrazone was precipitated in the wash-bottles; it (0·25 g., 60%) had m. p. 160°, and after crystallisation 165—167° alone or mixed with authentic material. The residue in the reaction flask yielded di-*p*-methoxyphenylmethane (0·28 g., 67%), m. p. and mixed m. p. 48—50°, and di-*p*-methoxyphenyl ketone (0·02 g.), m. p. 138—140° (mixed with a pure specimen, m. p. 140—142°).

(*c*) A solution of the ethyl ether in aldehyde-free *n*-propanol (2 c.c.) containing hydrochloric acid (0·18 c.c.), after being heated under reflux for 9 hours, yielded *n*-propaldehyde 2 : 4-dinitrophenylhydrazone (0·15 g., 35%), m. p. 140—145°; recrystallisation from ethanol gave the pure compound, m. p. 154—155°, undepressed when mixed with an authentic specimen but depressed to <140° when mixed with acetaldehyde 2 : 4-dinitrophenylhydrazone. Di-*p*-methoxyphenylmethane (0·37 g., 88%), m. p. 46—48°, was isolated from the non-volatile reaction mixture.

Decomposition of Bisdi-p-methoxyphenylmethyl Ether in Acidified Ethanol.—A solution of the bis-ether (0·5 g.) in aldehyde-free ethanol (4 c.c.) containing hydrochloric acid (0·36 c.c.) was heated under reflux. A precipitate was rapidly formed in the wash-bottles and after 8 hours' heating acetaldehyde 2 : 4-dinitrophenylhydrazone (0·27 g., 57%) was collected and characterised. The non-volatile residue yielded di-*p*-methoxyphenylmethane (0·40 g., 83%), m. p. 48—50°, and di-*p*-methoxyphenyl ketone (0·08 g.), m. p. 135—140°.

Thermal Decomposition of Di-p-methoxyphenylmethyl Ethyl Ether.—The ethyl ether (1·27 g.) was heated in an oil-bath, carbon dioxide being passed through the flask and into wash-bottles as before. When the temperature reached 300° a precipitate began to form in the wash-bottles and after 7 hours' heating amounted to 0·10 g. (10%); it had m. p. 160—162° alone and when mixed with an authentic specimen of acetaldehyde 2 : 4-dinitrophenylhydrazone. The non-volatile material yielded di-*p*-methoxyphenyl ketone (0·63 g.; 56%), m. p. and mixed m. p. 138—140°, resin (0·1 g.) and di-*p*-methoxyphenylmethane (0·25 g., 25%), m. p and mixed m p. 45—48°.

Action of Trichloroacetic Acid on Xanthhydrol.—(a) 3·5% *Acid.* A solution of xanthhydrol (1·0 g.) and trichloroacetic acid (0·07 g.) in dry benzene (2 c.c.), in an atmosphere of nitrogen, was kept at 40° for 2 hours. After cooling, crystals of xanthone separated (0·3 g.), m. p. 160—165° (after recrystallisation, 168—170°). The benzene mother-liquor was diluted with ether and washed with sodium hydroxide: after partial evaporation xanthone (0·09 g.), m. p. 167—170°, and xanthen (0·39 g.), m. p. 95—97°, both identified by mixed m. p.s, were collected.

A similar experiment in dioxan yielded xanthone (0·39 g.), m. p. 167—170°, and xanthen (0·35 g.), m. p. 96—98°.

(b) 0·1% *Acid.* To a solution of xanthhydrol (1·0 g.) in dry benzene (10 c.c.), trichloroacetic acid (0·01 g.) was added; subsequent procedure was as described above. Xanthone (0·35 g.), m. p. 168—172°, and xanthen (0·35 g.), m. p. 93—96°, were obtained.

In peroxide-free dioxan the products were unchanged xanthhydrol (0·55 g.) and dixanthyl ether (0·1 g.), m. p. and mixed m. p. 205—210° (after one recrystallisation).

Action of Acids on p-Methoxydiphenylmethanol.—(*a*) A solution of the alcohol (2·0 g.) inacetone (6 c.c.) containing hydrochloric acid (0·23 c.c., 0·5 mol.) was heated for 5 hours under gentle reflux, the air having been displaced by nitrogen. After the acetone had evaporated the residue was dissolved in ether, washed, and dried, and the solvent evaporated. Trituration of the residue with ether–light petroleum left di-(*p*-methoxydiphenylmethyl) ether (1·5 g.) which, after crystallisation, had m. p. and mixed m. p. 120—121°. The filtrate yielded *p*-methoxydiphenylmethane (0·15 g.), b. p. 125—130°/0·4 mm., and *p*-methoxybenzophenone (0·1 g.), b. p. 140—160°/0·4 mm., which crystallised on cooling; its 2 : 4-dinitrophenylhydrazone had m. p. and mixed m. p. 205°.

(*b*) A solution of the alcohol (1·0 g.) and toluene-*p*-sulphonic acid (0·4 g.) in benzene (10 c.c.) was heated under reflux (under nitrogen) for 5 hours. The isolated products were di-(*p*-methoxydiphenylmethyl) ether (0·5 g.), m. p. 120—121°, *p*-methoxydiphenylmethane (0·1 g.), and *p*-

methoxybenzophenone (0·12 g.), m. p. and mixed m. p. 59—61°. The identity of *p*-methoxydiphenylmethane was confirmed by its demethylation followed by benzoylation; the m. p. of the resulting *p*-benzylphenyl benzoate was not depressed on admixture with an authentic specimen, m. p. 86—87°.

Action of Acids on Di-p-dimethylaminophenylmethanol (Michler's Hydrol).—(a) *Trichloroacetic acid.* A solution of the alcohol (1·0 g.) and trichloroacetic acid (0·6 g.; 1 mol.) in acetone (5 c.c.), in an atmosphere of nitrogen, was kept at 40° for 4 hours. After 30 minutes the colour of the solution changed from blue to claret-red and crystals began to separate. The crystals (0·3 g.) consisted of the di-ether of Michler's hydrol and, after crystallisation had m. p. 195—197° alone or admixed with an authentic specimen prepared as described by Möhlau and Heinze (*Ber.*, 1902, **35**, 361). The decanted acetone solution yielded a further 0·05 g. of the di-ether, together with Michler's ketone (0·33 g.) and some tar.

(b) *Hydrochloric acid.* A solution of the alcohol (2·7 g.) in 2N-hydrochloric acid (10 c.c.) after 5 hours at 100° yielded Michler's ketone (0·73 g.) and the di-ether of Michler's hydrol (0·35 g.).

pp'-*Di*-tert.-*butylbenzophenone.*—Prepared by a Friedel–Crafts reaction from *tert.*-butylbenzene and carbonyl chloride in carbon disulphide, in 64% yield, this had m. p. 134—135° (Found: C, 85·8; H, 8·9. Calc. for $C_{16}H_{18}O$: C, 85·7; H, 8·85%). Cristal, Hayes, and Haller (*J. Amer. Chem. Soc.*, 1946, **68**, 913) record m. p. 134·5—135°.

Di-p-tert.-*butylphenylmethanol.*—A mixture of the foregoing ketone (10 g.), potassium hydroxide (6 g.), zinc dust (5 g.), and ethanol (100 c.c.) was heated under vigorous reflux for 6 hours and worked up as usual. The resulting *di*-p-tert.-*butylphenylmethanol* (9·7 g.) had m. p. 98—100°; it separated from ether–light petroleum in fine, silky needles, m. p. 103—104° (Found: C, 85·2; H, 9·4. $C_{21}H_{28}O$ requires C, 85·1; H, 9·4%).

Action of acids. A mixture of the alcohol (1·0 g.) and trichloroacetic acid (0·27 g., 0·5 mol.) was heated at 100°, the clear solution becoming semi-solid after a few minutes. After 30 minutes the product was washed with water and crystallised from ethanol–acetone: it consisted of *bisdi*-p-tert.-*butylphenylmethyl ether*, fine needles, m. p. 218—219° (Found: C, 88·2; H, 9·35. $C_{42}H_{54}O$ requires C, 87·8; H, 9·4%).

A solution of the alcohol (1·0 g.) in acetone (2 c.c.) containing hydrochloric acid (0·17 c.c., 0·5 mol.) was heated under reflux for 8 hours. The bis-ether (0·8 g.), m. p 216—218°, was readily isolated, but of a substituted benzophenone there was no trace

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144. *Some Observations on the Constitution of Gum Myrrh.*

By L. HOUGH, J. K. N. JONES, and W. H. WADMAN.

The isolation and characterisation of D-galactose, L-arabinose, and 4-methyl D-glucuronic acid as components of gum myrrh are described.

GUM MYRRH, like frankincense, gum asafœtida, and gum gamboge, is a typical oleo-gum-resin, and is composed mainly of carbohydrate, protein, and terpenoid resins (Hirst and Jones, *Research*, 1951, **4**, 411). The substance has been used as incense for many centuries. In more recent times, the gum has found medical usage as an antiseptic, the tincture being applied to inflammatory and ulcerated conditions of the throat and mouth (cf. Trease, "A Textbook of Pharmacognosy," 5th Edn., Bailliere, Tindall, and Cox, p. 356). The gum-resin is exuded from cracks and fissures in the bark of *Commiphora myrrha* Holmes (fam. Burseraceae) found in N.E. Africa and Arabia, forming nodules composed of a red oily resin and white streaks of gum. On extraction with 90% aqueous alcohol, the resins are largely removed and the crude polysaccharide thus obtained (*ca.* 40% yield) may be further purified by precipitation from acidified alcohol. A crude acidic polysaccharide prepared in this manner had an equivalent weight of 547, and contained 6·1% of methoxyl. The product gave positive tests for amino-acids and from the nitrogen content was estimated

to contain approximately 18% of protein. After its hydrolysis with acid, at least fifteen amino-acids were detected on the paper chromatogram.

Addition of copper sulphate to an aqueous solution of the alcohol-insoluble material precipitated most of the polysaccharide as an insoluble copper complex. The remainder of the polysaccharide was then precipitated from solution by the addition of alcohol. The two fractions, after removal of the copper, were obtained as cream-coloured, amorphous materials, designated the copper-insoluble polysaccharide *A* (yield, 70%) and the soluble polysaccharide *B* (yield, 19%). An examination of their hydrolysis products on the paper chromatogram indicated that each of these fractions contained galactose, arabinose, and a monomethyl uronic acid. After removal of the uronic acid component, quantitative determination by the periodate oxidation procedure of Hirst and Jones (*J.*, 1949, 1659) showed the presence of approximately 5% of arabinose and 20% of galactose (calculated as $C_5H_8O_4$ and $C_6H_{10}O_5$ respectively) in each fraction. The fractions contained protein, approximately 15% in *A* and 20% in *B*, as estimated from their nitrogen contents, and possibly adherent resin. Determination of the equivalent weights by alkaline titration gave a figure of 507 for the copper-insoluble polysaccharide *A* and 678 for the soluble polysaccharide *B*; calculation from the methoxyl contents, on the assumption that the acidic component was wholly monomethyl hexuronic acid, gave equivalent weights of 492 and 705 respectively, which are in fair agreement with those obtained by titration. Since these results show that there may be some difference in the carbohydrate moiety of these fractions, it is clear that further investigation of the homogeneity of gum is essential before the inception of structural studies.

In order to separate and hence finally to identify the two neutral sugars and the partly methylated uronic acid, a large-scale hydrolysis of the acidic polysaccharide, followed by a separation of the liberated neutral sugars from the uronic acid component, was performed, the acid being absorbed on the anion-exchange resin, Amberlite IR-4B. Crystalline specimens of D-galactose and L-arabinose were obtained by counter-current partition of the mixture of neutral reducing sugars between *n*-butanol and water in a cellulose-packed column (Hough, Jones, and Wadman, *J.*, 1949, 2511).

The partly methylated uronic acid was recovered from the ion-exchange resin by displacement with mineral acid. Examination of this fraction on the sheet-paper chromatogram indicated the presence of a substance which gave a characteristic brilliant-red colour on treatment with the *p*-anisidine spray reagent and moved at the rate of a monomethyl uronic acid.

Since the known methylated derivatives of the uronic acids are few, whereas in comparison the methylated derivatives of the corresponding neutral aldose derivatives are well characterised, the uronic acid was converted into its methyl ester methylglycuronoside, the carbomethoxy-group of which was then reduced with lithium aluminium hydride (Lythgoe and Trippett, *J.*, 1950, 1983) to the corresponding primary alcohol. The resultant neutral monomethyl methylglycoside was then converted by hydrolysis into the monomethyl hexose. The latter was a glucose derivative since demethylation with 48% hydrobromic acid furnished this sugar, identified by its rate of movement and colour reactions on the paper chromatogram. This was confirmed by methylation of the methylglycoside, followed by hydrolysis of the product, which sequence of operations afforded crystalline 2 : 3 : 4 : 6-tetramethyl D-glucose. It is clear then that the methoxy-group of the monomethyl glucose must be situated on $C_{(2)}$, $C_{(3)}$, or $C_{(4)}$, and an examination of the sugar on the paper chromatogram showed its rate of movement and colour reaction to be indistinguishable from those of 4-methyl D-glucose but different from those of 2- and 3-methyl D-glucose. Confirmation was provided by the formation of 4-methyl D-glucosazone, identical with an authentic specimen kindly supplied by Professor F. Smith of the University of Minnesota. It follows, therefore, that the original uronic acid present in gum myrrh must be 4-methyl D-glucuronic acid (CHO = 1).

A consideration of the above results for the crude acidic polysaccharide isolated from gum myrrh suggests that it contains approximately 64% of carbohydrate, and 18% of protein, the remainder (18%) being unidentified. The carbohydrate moiety contains the following monosaccharides in approximately the proportions indicated: D-galactose

(4 parts), L-arabinose (1 part), and 4-methyl D-glucuronic acid (3 parts). The occurrence of D-galactose and L-arabinose in gum myrrh is not unusual since these sugars are often encountered in close association in a wide variety of plant materials. On the other hand, the occurrence of 4-methyl D-glucuronic acid in a complex polysaccharide is of great interest, since the acidic component of these materials is usually found to be galacturonic, glucuronic, or mannuronic acid (Jones and Smith, *Adv. Carbohydrate Chem.*, 1949, **4**, 243) and hitherto in one instance only has a methylated uronic acid been obtained from a natural product—mesquite gum, from which White (*J. Amer. Chem. Soc.*, 1948, **70**, 367 and Smith (*J.*, 1951, 2646) isolated the same component, 4-methyl D-glucuronic acid. Monomethyl uronic acids are reported to occur in the hemicellulose of jute fibre (Sarker, *Nature*, 1951, **167**, 357) and of American White Oak (O'Dwyer, *Biochem. J.*, 1923, **17**, 503) but as yet remain unidentified. It may well be that methylated sugars and uronic acids are of more common occurrence in natural products than is usually supposed. Recent work (unpublished) has indicated that several gums contain partly methylated monosaccharides, *e.g.*, grapefruit gum, lemon gum, Chile plum gum, and golden apple gum. The methylated neutral sugars hitherto encountered in Nature are of the 3-methyl type (cf. Hirst, Hough, and Jones, *J.*, 1951, 323).

Experimental

Isolation of the Polysaccharide.—The natural gum resin (430 g.) was extracted with 90% aqueous alcohol for removal of resins, and the residual crude polysaccharide, after dissolution in 20% alcohol, was slightly acidified with dilute hydrochloric acid and filtered into a large volume of alcohol. The insoluble acidic polysaccharide thus obtained was repeatedly reprecipitated in this manner from 20% aqueous alcohol until chloride-free, and the resultant product was dried at 60° under reduced pressure to give a light brown, friable powder (161 g.), $[\alpha]_D$ + 7° (*c*, 3·6 in water; neutral sodium salt) [Found : Sulphated ash, 1·6; N, 2·9; S, trace; OMe, 6·1%; equiv. (by alkaline titration), 547].

Fractionation by Formation of a Copper Complex.—The acidic polysaccharide (3·6 g.) was suspended in water (250 c.c.), and ammonia (*ca.* 2N) added with vigorous shaking until the solution was neutral; a little undissolved material was then removed on the centrifuge. A solution of copper sulphate (10%; 100 c.c.) was added to the supernatant liquid, and the resultant insoluble copper complex was removed on the filter. The filtrate was evaporated to a small volume (*ca.* 25 c.c.), whereafter the addition of methanol (250 c.c.) resulted in the precipitation of the water-soluble material, which was then isolated on the filter. The copper-insoluble and the soluble fraction were freed from copper by repeated washings on the filter with cold methanolic hydrogen chloride (5%) until the filtrate was copper-free. The mineral acid was removed from the polysaccharide by repeated washing with methanol until the washings were chloride-free. The products were dried at 60° under reduced pressure. The copper-insoluble fraction *A* (2·5 g.) had $[\alpha]_D$ +18° (*c*, 0·77 in water) [Found : OMe, 6·3; N, 2·5; sulphated ash, 2·1%; equiv. (by titration with standard alkali), 507]. The yield of soluble fraction *B* (was 0·7 g.) [Found : OMe, 4·4; N, 4·2; sulphated ash, 2·2%; equiv. (by titration with standard alkali), 678]. Each fraction gave positive tests for protein.

A qualitative examination of the hydrolysis products of these two fractions on the paper chromatogram (for methods see Hough, Jones, and Wadman, *J.*, 1950, 1702) suggested the presence of galactose, arabinose, and a monomethyl uronic acid. A quantitative estimate of the non-acidic reducing sugars was obtained in the following manner. The copper-insoluble polysaccharide *A* (186 mg.) was hydrolysed in a sealed tube with N-sulphuric acid (5 c.c.) for 16 hours at 100°. The reaction mixture was then washed into a flask containing rhamnose hydrate (67 mg.). Amberlite resin IR-4B was then added portion-wise, with shaking, until the solution was neutral, whereupon the resin was removed by filtration and the filtrate evaporated to a small volume (*ca.* 1 c.c.). A portion of the sugars was separated on the chromatogram and the position of the sugars located as described for quantitative analysis by Hirst and Jones (*loc. cit.*). The paper strips holding the galactose, arabinose, and rhamnose were then extracted with water and the quantities of sugars determined by periodate oxidation (*idem, ibid.*) (Found : 5·09, 1·09, and 8·37 mg. of these sugars respectively). From these figures, the recovery of rhamnose being assumed to be quantitative, the copper-insoluble fraction contains 21·9% of galactose and 4·7% of arabinose (calc. as $C_6H_{10}O_5$ and $C_5H_8O_4$ respectively). In a similar manner, the soluble fraction *B* (94·5 mg.) was hydrolysed, rhamnose hydrate (45·2 mg.) added, and the mixture of sugars analysed (Found : galactose, 1·46 mg.; arabinose, 0·41 mg.; rhamnose, 3·73 mg.).

Thus this fraction contains 19·6% of galactose and 5·2% of arabinose (calc. as $C_6H_{10}O_5$ and $C_5H_8O_4$ respectively).

Large-scale Hydrolysis of the Polysaccharide.—The purified polysaccharide (40 g.) was dissolved in 0·5N-sulphuric acid (1·6 l.) and heated under reflux on a boiling water-bath, the hydrolysis being followed polarimetrically: $[\alpha]_D$ +7° (initial value), +42° (3·5 hours), +54° (6 hours), +56° (8 hours), +65° (11 hours). After 18 hours, the dark-brown solution was cooled and Amberlite Resin IR-4B added portion-wise, with stirring, until the solution was neutral. This mixture of resin and solution was slowly introduced into a column (2 × 24 in.) containing at the base a small bed (2 in.) of fresh Amberlite Resin IR-4B to remove any residual acidity. The solution was allowed to percolate down the column, followed by water until the effluent was non-reducing. The effluents were concentrated, treated with charcoal, filtered, and evaporated to a syrup *C* (31 g.).

The uronic acids were recovered by stirring the resin with dilute sulphuric acid portion-wise until a permanent excess of sulphuric acid was present. The resin was then washed with water until the washings were both non-reducing and sulphate-free. To the filtrate barium acetate solution was added with stirring from a burette until the solution was just sulphate-free, the insoluble barium sulphate was removed on the filter, and the filtrate concentrated under reduced pressure to a syrup *D* (15 g.).

Examination of the non-acidic reducing sugars (C). A preliminary examination of the syrup on the paper chromatogram using a variety of solvents indicated the presence of only two sugars, which were provisionally identified by their rates of movement and colour reactions as galactose and arabinose; uronic acids were not detected. Confirmation was provided by the separation of a portion of this syrup (1·27 g.) by partition chromatography on a column of cellulose powder with butanol–water as the mobile phase (Hough, Jones, and Wadman, *loc. cit.*). A complete separation was obtained; the first fraction gave crystalline L-arabinose (0·63 g.), m. p. and mixed m. p. 158°, $[\alpha]_D$ +96° (*c*, 0·48 in water; equilibrium value); the other fraction gave crystalline D-galactose (0·56 g.), m. p. 161°, $[\alpha]_D$ +82° (*c*, 1·4 in water; equilibrium value), which yielded the characteristic *N*-methyl-*N*-phenylhydrazone (m. p. 185°).

Examination of the acidic sugars (D). The syrup, $[\alpha]_D$ 45° (*c*, 5·8 in water) (Found: OMe, 13·9. Calc. for monomethyl hexuronic acid, OMe, 14·2%), was examined on the paper chromatogram; *n*-butanol saturated with water, to which formic acid had been added to a concentration of 5%, was used as the mobile phase; after separation and evaporation of the solvents the chromatogram was sprayed with a solution of *p*-anisidine hydrochloride in *n*-butanol (*idem, ibid.*) and heated. This reagent gave a bright red spot (R_F 0·28) corresponding to a monomethyl hexuronic acid, and showed faint spots corresponding to galactose and arabinose; no unsubstituted hexuronic acid could be detected.

Methyl Ester Methyl Hexuronoside.—The syrupy monomethyl hexuronic acid was converted into the methyl ester methyl hexuronoside by heating the syrup (6 g.) in 4% methanolic hydrogen chloride at 100° for 8 hours. After cooling, the solution was neutralised by the addition of silver carbonate, the insoluble silver salts were removed on the filter, and the filtrate was concentrated under reduced pressure to a syrup (6·85 g.) (Found: OMe, 38·7. Calc. for the methyl ester of a monomethyl methyl hexuronoside: OMe, 39·4%).

Reduction with lithium aluminium hydride. The methyl glycuronoside methyl ester (1 g.) in tetrahydrofuran was reduced with lithium aluminium hydride, under the conditions specified by Lythgoe and Trippett (*loc. cit.*). The resultant complex was decomposed by pouring the mixture into ice-cold dilute sulphuric acid, after which the solution was neutralised by the addition of barium carbonate, filtered, and evaporated under reduced pressure; the solid residue was then extracted exhaustively with hot methanol. Evaporation of the methanol extract afforded syrupy monomethyl methylhexoside (0·62 g.) (Found: OMe, 28·5. Calc. for $C_8H_{16}O_6$: OMe, 29·8%).

Methylation of the monomethyl methylhexoside. A portion (99 mg.) of the foregoing syrup was repeatedly methylated with Purdie's reagents, and after five treatments yielded tetramethyl methylhexoside (104 mg.), n_D^{18} 1·4470, which on hydrolysis yielded 2 : 3 : 4 : 6-tetramethyl D-glucose, m. p. and mixed m. p. 83°, $[\alpha]_D$ +83° (c, 1·2 in water) (61 mg.). The *X*-ray powder photograph of the crystals was identical with that of an authentic specimen.

Hydrolysis of the monomethyl methylhexoside. Hydrolysis of a portion (0·51 g.) in 0·5N-sulphuric acid (25 c.c.) at 100° for 3 hours gave, after neutralisation with barium carbonate, a syrupy monomethyl hexose (0·44 g.), $[\alpha]_D$ +63° (*c*, 2·0 in water) (Found: OMe, 17·5. Calc. for a monomethyl hexose: OMe, 16·0%).

Demethylation of the monomethyl hexose. A portion (*ca.* 5 mg.) of this sugar was demethylated

by heating a solution in hydrobromic acid (48% w/v; 0·5 c.c.) in a sealed tube at 100° for 6 minutes, and the products were isolated in the usual manner (Hough, Jones, and Wadman, *loc. cit.*). Examination of this material on the paper chromatogram showed it to contain the original monomethyl hexose and a sugar indistinguishable from glucose.

Examination of the monomethyl sugar on paper chromatograms, using a variety of solvents, showed one discrete spot in all cases corresponding exactly in position and colour reactions with those shown by authentic 4-methyl glucose and clearly distinguishable from 2-, 3-, and 6-methyl glucose. Thus, for example, in butanol–pyridine–water (3 : 1 : 1 v/v) 2-, 3-, 4-, and 6-monomethyl glucoses had R_F values of 0·235, 0·260, 0·285, and 0·275 respectively (obtained by comparison with rhamnose, the R_F of which was assumed to be 0·300).

Formation of 4-*methyl* D-*glucosazone.* A portion (54 mg.) of the monomethyl hexose was dissolved in water (2 c.c.) containing phenylhydrazine (0·2 c.c.) and glacial acetic acid (0·2 c.c.). The mixture was heated at 60—70° for 3 hours. The osazone was isolated, washed with a little benzene and recrystallised from ethyl alcohol–water and then from benzene; it (51 mg.) had m. p. 157° and $[\alpha]_D$ +27° (initial value)→ +3° (20 hours; constant value) and was identical in crystal form with a genuine specimen of 4-methyl D-glucosazone, m. p. 158—159°, $[\alpha]_D$ +32° → 0°, and the *X*-ray powder photographs were indistinguishable (Found: OMe, 8·2. Calc. for monomethyl hexosazone, OMe, 8·3%).

We thank Professor F. Smith for the sample of 4-methyl D-glucosazone, Dr T. Bevan for the *X*-ray examination, and the Colston Research Society for a grant. One of us (W. H. W.) thanks the Department of Scientific and Industrial Research for a maintenance grant.

THE UNIVERSITY, BRISTOL. [*Received, November 8th,* 1951.]

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145. *Coenzyme A. Part V.* A New and Convenient Synthesis of Pantetheine* (Lactobacillus bulgaricus *Factor*).

By J. BADDILEY and E. M. THAIN.

Pantetheine (*Lactobacillus bulgaricus* factor) (I) has been prepared in good yield by an adaptation of the Bergmann peptide synthesis. Reaction of carbobenzyloxy-β-alanine azide with 2-benzylthioethylamine (III) gave the amide (IV). Benzyl and carbobenzyloxy-groups were removed by reduction with sodium in liquid ammonia, and the resulting amino-thiol, *N*-β-alanyl-2-mercaptoethylamine (V) on being heated with D(−)-pantolactone gave pure pantetheine directly.

A GROWTH factor for *Lactobacillus bulgaricus* was isolated from natural materials by McRorie, Masley, and Williams (*Arch. Biochem.*, 1950, **27**, 471) and by Brown, Craig, and Snell (*ibid.*, p. 473). It was recognised as a pantothenic acid derivative and shown later by synthesis to possess the structure (I). Originally called the "*L. bulgaricus* factor" (LBF), the names pantetheine and pantethine have been suggested by Snell and his collaborators for the two interconvertible forms (I) and (II) in which the growth factor is known to exist (Snell, Brown, Peters, Craig, Wittle, Moore, McGlohon, and Bird, *J. Amer. Chem. Soc.*, 1950, **72**, 5349). The synthesis involved reaction between methyl pantothenate and 2-mercaptoethylamine and the yield of biologically active material was less than 10% before purification. The final isolation of the synthetic material in a state of purity involved partition chromatography and counter-current distribution which are not well adapted to laboratory-scale preparation (Snell *et al.*, *loc. cit.*).

$$HO{\cdot}CH_2{\cdot}CMe_2{\cdot}CH(OH){\cdot}CO{\cdot}NH{\cdot}CH_2{\cdot}CH_2{\cdot}CO{\cdot}NH{\cdot}CH_2{\cdot}CH_2{\cdot}SH \quad (I)$$

$$[HO{\cdot}CH_2{\cdot}CMe_2{\cdot}CH(OH){\cdot}CO{\cdot}NH{\cdot}CH_2{\cdot}CH_2{\cdot}CO{\cdot}NH{\cdot}CH_2{\cdot}CH_2{\cdot}S]_2 \quad (II)$$

Our interest in this substance was aroused by its established relation to coenzyme A (Brown, Craig, and Snell, *loc. cit.*; Baddiley and Thain, *Chem. and Ind.*, 1951, 337; *J.*, 1951, 2253) in which it is probably attached through a pyrophosphate linkage involving the

* Part IV, *J.*, 1951, 3425.

primary hydroxyl group to adenosine-2′(or 3′) : 5′ diphosphate. As we required quantities of this substance, not only for biological studies, but also as an intermediate in various synthetic experiments an improved synthesis seemed desirable. In view of the difficulties encountered in the first synthesis an alternative route giving high yields would also dispel any doubts as to the correctness of the structures (I) and (II).

It seemed likely that one drawback of the synthesis was the rather unreactive nature of methyl pantothenate towards amines and the subsequent difficulty in removing unchanged ester. Our synthesis therefore envisaged reaction between the more reactive pantolactone and *N*-β-alanyl-2-mercaptoethylamine (V).

For the preparation of the amine (V) we adapted the Bergmann peptide synthesis in a manner similar to that suggested by Sifferd and du Vigneaud (*J. Biol. Chem.*, 1935, **108**, 753) for sulphur-containing peptides. 2-Benzylthioethylamine (III) was prepared in almost quantitative yield by reaction of 2-bromoethylamine hydrobromide and toluene-ω-thiol in the presence of sodium ethoxide in alcohol, a very considerable improvement on the earlier method (Michels, *Ber.*, 1892, **25**, 3048). Sodium in liquid ammonia removed the benzyl group from (III), giving 2-mercaptoethylamine (cysteamine), also in high yield. This is the most convenient method for the preparation of 2-mercaptoethylamine. Reaction of (III) with carbobenzyloxy-β-alanine azide in chloroform gave an excellent yield of 2-benzylthio-*N*-(carbobenzyloxy-β-alanyl)ethylamine (IV), from which the benzyl and the carbobenzyloxy-group were removed by reduction with sodium in liquid ammonia. The resulting *N*-β-alanyl-2-mercaptoethylamine (V) was almost pure as isolated from the reaction mixture, but final purification was effected by vacuum-sublimation. The structure of the amino-thiol was established by acetylation to the *SN*-diacetyl compound which was shown to be identical with that prepared by condensing *N*-acetyl-β-alanine methyl ester with 2-mercaptoethylamine and acetylating the product (Baddiley and Thain, *J.*, 1951, 3425). The free thiol (V) was unstable in air, being readily oxidised to the disulphide (VI).

(III) $H_2N{\cdot}CH_2{\cdot}CH_2{\cdot}S{\cdot}CH_2Ph$ $\quad$ $Ph{\cdot}CH_2{\cdot}O{\cdot}CO{\cdot}NH{\cdot}CH_2{\cdot}CH_2{\cdot}CO{\cdot}NH{\cdot}CH_2{\cdot}CH_2{\cdot}S{\cdot}CH_2Ph$ (IV)

(V) $H_2N{\cdot}CH_2{\cdot}CH_2{\cdot}CO{\cdot}NH{\cdot}CH_2{\cdot}CH_2{\cdot}SH$ $\quad$ $(H_2N{\cdot}CH_2{\cdot}CH_2{\cdot}CO{\cdot}NH{\cdot}CH_2{\cdot}CH_2{\cdot}S)_2$ (VI)

D(−)Pantolactone reacted readily with *N*-β-alanyl-2-mercaptoethylamine (V) at 100° in the absence of solvent. The product was indistinguishable from pantetheine when examined by paper chromatography, only traces of impurities being detected. When tested as a growth stimulant for *L. bulgaricus* it showed an activity of 26 000 units/mg. Snell *et al.* (*J. Amer. Chem. Soc.*, *loc. cit.*) report an activity of about 29 000 units/mg. which suggests that their preparation is somewhat purer. However, the accuracy of such methods is rather limited.

Experimental

2-Benzylthioethylamine Hydrochloride.—Powdered 2-bromoethylamine hydrobromide (10·25 g.) was added to a solution of toluene-ω-thiol (6·2 g.) and sodium (2·3 g.) in alcohol (50 c.c.), and the resulting mixture was refluxed in an atmosphere of nitrogen for 1·5 hours. Sodium bromide was filtered off and washed well with alcohol. Filtrate and washings were combined, acidified with concentrated hydrochloric acid, and evaporated to dryness under reduced pressure. The crystalline residue was dissolved in warm *iso*propyl alcohol, filtered, and evaporated under reduced pressure. The residue consisted of almost pure 2-benzylthioethylamine hydrochloride (10·2 g.). Recrystallised from *n*-butyl alcohol it formed prisms, m. p. 119—120° (Found: C, 53·7; H, 7·4; N, 7·1; S, 15·8. Calc. for $C_9H_{14}NSCl$: C, 54·1; H, 6·9; N, 6·9; S, 15·8%). It was converted in the usual way into a benzoyl derivative, m. p. 78°, for which Michels (*loc. cit.*) reports m. p. 78—80°.

2-Mercaptoethylamine.—Sodium in small pieces was added to a solution of 2-benzylthioethylamine hydrochloride (10 g.) in liquid ammonia (*ca.* 150 c.c.) with gentle swirling until a deep blue colour persisted in the solution for at least 45 minutes. Excess of sodium was destroyed by addition of a little ammonium chloride, and ammonia was then removed by evaporation under reduced pressure. The solid residue was dissolved rapidly in iced water and acidified by cautious addition of concentrated hydrochloric acid. Water was removed by evaporation and the dry residue extracted with hot *iso*propyl alcohol (2 × 75 c.c.). The filtered solution

was evaporated to dryness, the residue redissolved in a little *iso*propyl alcohol, and the solution filtered and evaporated. The remaining syrup which crystallised on being rubbed consisted of fairly pure 2-mercaptoethylamine hydrochloride, m. p. *ca.* 40° (5·4 g., 97%). A sample was converted into the free base by treatment of a solution in methanol with the calculated amount of sodium in methanol, filtration, and evaporation. The base was purified by sublimation at 0·1 mm. It melted at 98—99°, undepressed on being mixed with an authentic sample, m. p. 99°.

*2-Benzylthio-*N*-(carbobenzyloxy-β-alanyl)ethylamine.*—A solution of 2-benzylthioethylamine hydrochloride (5 g.) in water (25 c.c.) was treated with a slight excess of 10% sodium hydroxide solution, the liberated 2-benzylthioethylamine extracted with chloroform, and the solution dried (Na_2SO_4). To this was added a freshly prepared dry chloroform solution of carbobenzyloxy-β-alanine azide, prepared from carbobenzyloxy-β-alanylhydrazide (6 g.) by the method of Sifferd and du Vigneaud (*loc. cit.*). The resulting yellow solution was set aside at room temperature for 20 hours with the exclusion of moisture. Chloroform and hydrazoic acid were removed by evaporation under reduced pressure and the crystalline residue was recrystallised from aqueous alcohol. *2-Benzylthio-*N*-(carbobenzyloxy-β-alanyl)ethylamine* formed plates, m. p. 122—123° (8·2 g., 91%) (Found: C, 64·3; H, 6·0; N, 7·4; S, 8·9. $C_{20}H_{24}O_3N_2S$ requires C, 64·6; H, 6·5; N, 7·5; S, 8·6%).

N-β-Alanyl-2-mercaptoethylamine.—The dry, finely powdered carbobenzyloxy-compound (12 g.) was added in portions to liquid ammonia (*ca.* 150 c.c.). To the suspension was added sodium in small pieces with occasional agitation. As the sodium dissolved, suspended carbobenzyloxy-compound went into solution, then later a solid was deposited. Addition of sodium was continued until the resulting blue solution maintained its colour for at least 45 minutes. Excess of sodium was destroyed by ammonium chloride, and ammonia removed by evaporation under reduced pressure. The solid residue was dissolved in iced water, and the solution acidified (Congo-red) with concentrated hydrochloric acid. Insoluble material was extracted with ether, and the aqueous solution evaporated to dryness under reduced pressure. The dry, powdered residue was extracted with 3 lots of boiling *iso*propyl alcohol (total 200 c.c.), which was then filtered while hot and evaporated to dryness under reduced pressure. This was repeated with a second portion (60 c.c.) of *iso*propyl alcohol. The syrupy residue (6 g., quantitative) was almost pure *hydrochloride* of the amino-thiol (V) (Found: Cl, 19·3. $C_5H_{13}ON_2SCl$ requires Cl, 19·3%). A solution of this salt in alcohol when kept under nitrogen slowly deposited crystals. Recrystallised from 95% alcohol the pure salt had m. p. 214—217° (Found: C, 33·0; H, 6·8; N, 14·7; S, 17·0. $C_5H_{13}ON_2SCl$ requires C, 32·6; H, 7·0; N, 15·1; S, 17·3%). A solution of the hydrochloride (5·8 g.) in methanol (50 c.c.) was mixed with a solution of sodium (0·72 g.) in methanol (20 c.c.). After 10 minutes at room temperature sodium chloride was removed and the filtrate evaporated under reduced pressure to a syrup. This was dissolved in hot *iso*propyl alcohol (40 c.c.), and the solution was filtered and evaporated to dryness. The syrupy residue slowly crystallised. *N-β-Alanyl-2-mercaptoethylamine* obtained in this way had m. p. 88—90° and was pure enough for conversion into pantetheine (yield, almost quantitative). A sample sublimed at 140°/10^{-5} mm. had m. p. 93—95° (Found: C, 40·5; H, 8·1; N, 18·3; S, 20·8. $C_5H_{12}ON_2S$ requires C, 40·5; H, 8·1; N, 18·8; S, 21·5%). The base gave a positive nitroprusside reaction and decolorised a solution of iodine in potassium iodide and so must be a thiol. Longer storage of solutions of the free base deposited the amorphous disulphide.

SN-Diacetyl-β-alanyl-2-mercaptoethylamine.—Freshly sublimed, powdered *N*-β-alanyl-2-mercaptoethylamine (0·2 g.) was heated with acetic anhydride (2 c.c.) on a steam-bath for 1 hour. Acetic anhydride was then removed by evaporation under reduced pressure, and the residue was treated with water. *SN*-Diacetyl-β-alanyl-2-mercaptoethylamine, recrystallised from ethyl acetate, had m. p. 139—140°, somewhat higher than was found for the earlier sample (Baddiley and Thain, *J.*, 1951, 3425), but the m. p.s of the samples were undepressed on admixture.

Pantetheine.—D(−)-Pantolactone (1·75 g.) and *N*-β-alanyl-2-mercaptoethylamine (2·0 g.) were heated on a steam-bath for 2·5 hours in an atmosphere of nitrogen. The resinous product was triturated with ether, then traces of solvent were removed under reduced pressure. The yield was quantitative. Examination of this product by paper chromatography as described below indicated that it was essentially homogeneous; it possessed full biological activity. Further purification for analysis was effected by a 12-stage counter-current distribution in *n*-butyl alcohol–water–acetic acid (4 : 5 : 1). Pantetheine was concentrated mainly in fractions 4, 5, and 6. Evaporation of these combined fractions left a resin, $[\alpha]_D^{20}$ +12·9° (*c*, 4·5 in water) (Found: C, 46·8; H, 8·1; N, 9·8; S, 11·0. Calc. for $C_{11}H_{22}O_4N_2S$: C, 47·5; H, 7·9; N, 10·1; S, 11·5%). This probably contains traces of moisture because of its resinous and hygroscopic nature.

Paper Chromatography of Pantetheine.—Ascending-front chromatography on Whatman No. 1 paper was carried out by the usual methods in the following solvent mixtures: *n*-butanol–water, amyl alcohol–water, *n*-butanol–water–acetic acid (4 : 5 : 1). No special precautions were taken for temperature control since substances for comparison were always run alongside those under examination. The following were examined, pantetheine (not purified) as prepared above, synthetic pantetheine (solution in *n*-butanol supplied by Parke, Davis & Co.), pantetheine purified by counter-current distribution, *N*-β-alanyl-2-mercaptoethylamine, and 2-mercaptoethylamine. After the solutions had run overnight, solvent was evaporated from the papers in a steam-oven, and substances were detected by both ninhydrin and cyanide–nitroprusside spraying. The R_F are shown in the Table.

	BuOH–H_2O	BuOH–AcOH	C_5H_{11}·OH–H_2O
Pantetheine (unpurified)	0·7	0·75	0·55
,, (purified)	—	0·75	—
,, (Parke Davis)	0·7	0·75	0·55
N-β-Alanyl-2-mercaptoethylamine	0—0·4	0·1	0—0·15
2-Mercaptoethylamine	0—0·4	0·1	0—0·3

A faint, slow-moving spot, R_F 0·37 in butanol–acetic acid-water and 0·21 in butanol–water, was observed with both the unpurified pantetheine and the Parke, Davis sample, but this was absent from the sample purified by counter-current distribution. In butanol–water and in amyl alcohol–water considerable tailing of 2-mercaptoethylamine and *N*-β-alanyl-2-mercaptoethylamine was observed. This did not occur in butanol–acetic acid–water which produced clear spots of all substances examined. In our hands the cyanide–nitroprusside spray was very satisfactory and sensitive, but the ninhydrin spray was rather insensitive with these compounds, particularly with pantetheine.

Sincere thanks are offered to Drs. F. Lipmann and W. L. Williams for the growth tests and to Dr. L. A. Sweet of Parke, Davis & Co., Detroit, for a sample of pantetheine. We thank also the Department of Scientific and Industrial Research for a Special Research Grant.

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146. *Synthesis of Fluoranthenes. Part IX.* 3-Methylfluoranthene.*

By S. HORWOOD TUCKER.

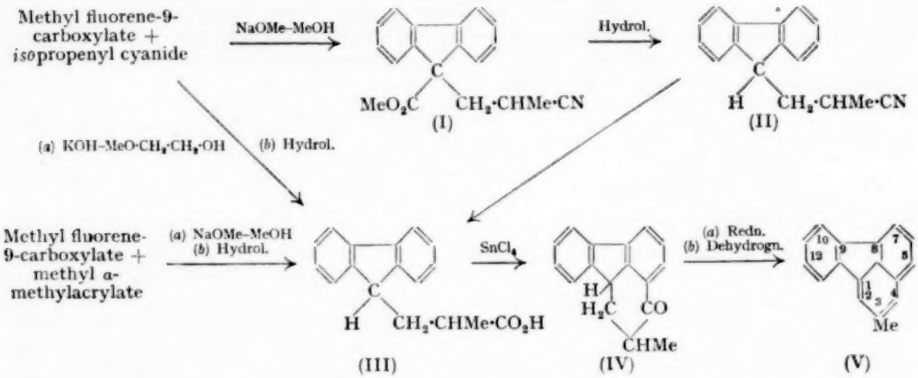
The Michael reaction between fluorene-9-carboxylates and vinyl cyanide and its derivatives has been improved by the use of sodium methoxide as reagent in methanolic solution. It has been found that αβ-unsaturated esters may be used with advantage instead of the vinyl cyanides. 3-Methylfluoranthene (V) has been synthesised from methyl fluorene-9-carboxylate by using both *iso*propenyl cyanide and methyl α-methylacrylate, and subsequently following the synthetic method developed in this series of papers.

THIS communication describes the synthesis of the last of the five isomeric monomethylfluoranthenes. The first to be prepared, 4-methylfluoranthene, was obtained by von Braun and Manz (*Ber.*, 1937, **70**, 1610; see further A. Campbell and Tucker, *J.*, 1949, 2623; Stubbs and Tucker, *J.*, 1950, 3288). 10- and 11-Methylfluoranthene were synthesised by Tucker and Whalley (*J.*, 1949, 3213; cf. Kloetzel and Mertel, *J. Amer. Chem. Soc.*, 1950, **72**, 4786) by the general method of Forrest and Tucker (*J.*, 1948, 1137). 2-Methylfluoranthene was synthesised by N. Campbell and Wang (*J.*, 1949, 1513), and also by the author (*J.*, 1949, 2182) using methyl fluorene-9-carboxylate and *n*-propenyl cyanide. Application of this general method has achieved the synthesis of 3-methylfluoranthene (V), as shown in the annexed scheme.

Formerly, in our general procedure for the Michael reaction we have used potassium hydroxide (0·2M) in dioxan or 2-methoxyethanol (*e.g.*, Tucker, *loc. cit.*), the latter solvent being preferable when hydrolysis of the intermediate cyano-compound to the carboxylic

* Part VIII, *J.*, 1951, 2939.

acid, without isolation of intermediates, is desired. But in this series Michael reactions in dioxan are slow and often incomplete. The use of sodium methoxide (0·2M) in methanol effects a decided improvement in the rate of reaction: the products either crystallise from the reaction mixture or can be readily isolated therefrom in high yields. This improved method has been used with vinyl, *n*-propenyl, and *iso*propenyl cyanides.



Acrylates have not hitherto been condensed with fluorene-9-carboxylates (cf. Michael and Ross, *J. Amer. Chem. Soc.*, 1930, **52**, 4598; Connor and Andrews, *ibid.*, 1934, **56**, 2713; Connor and McClellan, *J. Org. Chem.*, 1938, **3**, 570; Floyd and Miller, *ibid.*, 1951, **16**, 882), but we find that in presence of sodium methoxide in methanol this condensation proceeds readily with methyl acrylate, crotonate, and α-methylacrylate. Although the vinyl cyanides are usually more reactive than the acrylates, the addition products of the latter with the fluorene-9-carboxylates often crystallise from the reaction mixture more readily than do those of the cyanides, and are much more easily and rapidly hydrolysed in high yield to pure carboxylic acids.

Attempts to add ethyl tiglate or tiglic nitrile to the fluorene-9-carboxylates in presence of sodium or potassium alkoxide in the corresponding alcohol failed (cf. Michael and Ross, *loc. cit.*), varying amounts of methyl 9-hydroxyfluorene-9-carboxylate being obtained. Ethyl β-methylcrotonate and ethyl α-cyano-β-methylcrotonate also failed to combine with methyl fluorene-9-carboxylate.

Experimental

Direct Synthesis of β-9-*Fluorenyl*iso*butyric Acid* (III) *from Methyl Fluorene-9-carboxylate and Methyl* α-*Methylacrylate.*—Methyl fluorene-9-carboxylate (5·60 g., 1 mol.), anhydrous methanol (12·5 ml.), a solution of sodium (0·115 g., 0·2 atom) in methanol (11·5 ml.), and methyl α-methylacrylate (2·75 g., 1·1 mols.) were mixed in that order and left at *ca.* 20° for 24 hours. Cooling and scratching the solution failed to give crystals (cf. successful analogous examples, later), so the mixture was warmed and submitted to an air-blast to expel methanol as rapidly as possible. The residual oil was boiled with a mixture of 10N-potassium hydroxide (10 ml.) and 2-methoxyethanol (25 ml.) for 15 minutes, the solution poured into water, and the clear solution treated with concentrated hydrochloric acid and a few drops of glacial acetic acid. The crude solid crystallised very slowly from dioxan, but rapidly from light petroleum (b. p. 60—80°), forming rods, m. p. 137—139° (5·40 g., 85%), of β-9-*fluorenyl*iso*butyric acid* (III) (Found: C, 81·0; H, 6·2. $C_{17}H_{16}O_2$ requires C, 80·9; H, 6·4%). When the above reaction mixture was worked up after only 6 hours, the yield was 67%. The *methyl* ester of (III), prepared by use of methanol and hydrogen chloride, crystallised from acetic acid–water, then from methanol–water in cream-coloured prisms, m. p. 48—51° (Found: C, 81·3; H, 6·7. $C_{18}H_{18}O_2$ requires C, 81·2; H, 6·8%).

Stepwise Synthesis of β-9-*Fluorenyl*iso*butyric Acid* (III) *from Methyl Fluorene-9-carboxylate and* iso*Propenyl Cyanide.*—Methyl fluorene-9-carboxylate (5·60 g., 1 mol.), anhydrous methanol (12·5 ml.), sodium (0·115 g., 0·2 atom) in anhydrous methanol (11·5 ml.), and

*iso*propenyl cyanide (2·52 g., 1·5 mol.) were mixed and kept at 20° with occasional shaking. After 20 minutes the solution was clear, and after 5 hours a scratch started crystallisation. After being left overnight, the crystals were rinsed with methanol; the methanolic liquors gave more of the product. Recrystallisation from methanol gave soft crystals (typical of these cyano-esters) of *methyl* 9-2′-*cyano*-n-*propylfluorene*-9-*carboxylate* (I), m. p. 94—97° (6·54 g., 90%) (Found: C, 78·3; H, 6·0; N, 4·7. $C_{19}H_{17}O_2N$ requires C, 78·3; H, 5·9; N, 4·8%). Reduction of the relative proportion of *iso*propenyl cyanide (from 1·5 to 1·05 and to 1 mol.) caused a fall in yield (to 63 and 50%, respectively). When potassium hydroxide replaced sodium in the above reaction the yield of ester-cyanide (I) was 70%; but this must be considered a low estimate since recrystallisation was slow and wasteful. Potassium *tert.*-butoxide in benzene gave a 50% yield of (I). When potassium hydroxide (0·2 mol.) in dioxan was used, and the mixture kept for 14 days, the crystallised product (methanol) gave (I) in *ca.* 50% yield; methyl fluorene-9-carboxylate (*ca.* 50%) was recovered from the methanol filtrate. In this, and in corresponding experiments, dioxan is less favourable for the Michael reaction than the alcoholic solvents.

9-2′-*Cyano*-n-*propylfluorene*-9-*carboxylic Acid* (I; CO_2H for CO_2Me).—The ester-cyanide (I) (0·59 g.) was dissolved in ethanol, and 10N-potassium hydroxide added to the cold solution. After 5 minutes the solution became slightly milky; it was immediately extracted with ether, and excess of hydrochloric acid added to the aqueous portion. The nearly pure crystalline *acid* (0·49 g., 90%) recrystallised from benzene in burrs, losing benzene of crystallisation, and had m. p. 152—155° (softening at 150°) (Found: C, 78·2; H, 5·6; N, 4·9. $C_{18}H_{15}O_2N$ requires C, 78·0; H, 5·45; N, 5·05%).

Hydrolysis of Methyl 9-2′-*Cyano*-n-*propylfluorene*-9-*carboxylate* (I) *to* β-9-*Fluorenyl*-*iso*butyric *Acid* (III).—The ester-cyanide (I) (5·8 g.) and 10N-potassium hydroxide (20 ml.) in 2-methoxyethanol (30 ml.) were boiled for 2·5 hours, and poured into water. The clear solution, with concentrated hydrochloric acid, gave the acid (III), which after crystallisation from acetic acid–water and then from methyl cyanide had m. p. 137—139° (4·8 g., 95%). The use of 2-ethoxyethanol in place of 2-methoxyethanol gave a less pure product.

The acid (III) was also prepared directly from methyl fluorene-9-carboxylate (11·2 g., 1 mol.), *iso*propenyl cyanide (5·03 g., 1·5 mols.), and potassium hydroxide (0·56 g., 0·2 mol.) in 2-methoxyethanol (25 ml.); after 7 days, 10N-potassium hydroxide (75 ml.) and 2-methoxyethanol (50 ml.) were added, and the mixture was boiled vigorously for 4—5 hours and acidified as described for the corresponding preparation of β-9-fluorenylbutyric acid (Tucker, *loc. cit.*); the yield was 12·4 g. (98%).

1 : 2 : 3 : 4-*Tetrahydro*-4-*keto*-3-*methylfluoranthene* (IV).—A mixture of β-9-fluorenyl-*iso*butyric acid (III) (5·05 g.) and phosphorus pentachloride (5·05 g.) in benzene (25 g.; dried by phosphorus pentachloride) was boiled until evolution of hydrogen chloride ceased (*ca.* 15 minutes), cooled in ice, and added with shaking during 30 minutes to a solution of stannic chloride (5·5 ml.) in benzene (10 ml.) also kept ice-cold (Johnson and Glen, *J. Amer. Chem. Soc.*, 1949, **71**, 1094). After 2·5 hours in ice with occasional shaking, then at room temperature for 0·75 hour, the red liquid was treated several times with a mixture of concentrated hydrochloric acid and water (1 : 1 v/v) and with a small amount of ether. The pale yellow liquor obtained was washed with water, extracted with 5% sodium hydroxide solution (the extract gave a slight milky deposit with hydrochloric acid), washed with water just acid with hydrochloric acid, and evaporated to a pale yellow oil, which crystallised from light petroleum (b. p. 60—80°) and then from methyl cyanide to give 1 : 2 : 3 : 4-*tetrahydro*-4-*keto*-3-*methylfluoranthene* (IV; 3·78 g., 81%), m.p. 98—100° (Found: C, 87·4; H, 6·2. $C_{17}H_{14}O$ requires C, 87·15; H, 6·0%).

If the above cyclisation mixture was left overnight or over a week-end, yields of 62 and 45%, respectively, of (IV) were obtained. A preparation in which thionyl chloride was used instead of phosphorus pentachloride, and the mixture kept at room temperature overnight, gave a 43% yield of (IV). Use of aluminium chloride (1·1 mols.) instead of stannic chloride gave a gelatinous product which may have hindered complete utilisation of the catalyst; the yield was 45%. Hydrogen fluoride effected cyclisation in lower yield (30%) but the product, after once crystallising from methyl cyanide, as rod prisms, was pure (m. p. 98—100°).

The 2 : 4-*dinitrophenylhydrazone* of (IV), bright scarlet small crystals (from dioxan), had m. p. 251—254° (decomp.) (Found: C, 66·4; H, 4·6; N, 13·2. $C_{23}H_{18}O_4N_4$ requires C, 66·7; H, 4·4; N, 13·5%).

1 : 2 : 3 : 4-*Tetrahydro*-3-*methylfluoranthene*.—The ketone (IV) (1·17 g.), 90% hydrazine solution (2 ml.), and ethylene glycol (11 ml.) were boiled under reflux for 15 minutes, then gently distilled until water and excess of hydrazine had been removed (*ca.* 30 minutes). Potassium hydroxide (0·6 g.) was added to the cooled solution, which was boiled under reflux for 2 hours

(King and Nord, *J. Org. Chem.*, 1949, **14**, 638), then concentrated somewhat, treated with dilute hydrochloric acid, and extracted with ether, the ethereal extract evaporated, and the yellow, green-fluorescing oil so obtained chromatographed in light petroleum (b. p. 60—80°) through alumina and eluted with benzene. Two bright yellow bands were left on the column, and the benzene eluate gave a yellow oil (0·90 g.) which crystallised from acetic acid–water very slowly (*ca.* 7 days) in pale yellow rectangular plates, m. p. 48—50°, of 1 : 2 : 3 : 4-*tetrahydro*-3-*methylfluoranthene* (Found: C, 92·45; H. 7·3. $C_{17}H_{16}$ requires C, 92·7; H, 7·3%), which slowly became brown in air. It was also prepared by the Huang-Minlon process, diethylene glycol being used as solvent.

3-*Methylfluoranthene* (V).—The tetrahydromethylfluoranthene (0·84 g. as oil), chloranil (1·90 g.), and xylene (8 ml.) were boiled for 45 minutes. After cooling, crystals which separated were washed with benzene, and the filtrates combined and extracted twice with a mixture of sodium metabisulphite and 5% sodium hydroxide solutions, then with water. The benzene–xylene solution was evaporated, and the black residue extracted with boiling methanol; the solution gave salmon-tinted leaflets. The picrate (from methanol) was washed with sodium hydrogen carbonate solution, the pale brown residue dissolved in light petroluem (b. p. 60—80°), and the solution chromatographed (Al_2O_3; 10 cm.). Evaporation of the eluate gave after crystallisation from methanol ill-defined needles (0·56 g., 68%), m. p. 79—81°, of 3-*methylfluoranthene* (V) (Found: C, 94·6; H, 5·6. $C_{17}H_{12}$ requires C, 94·4; H, 5·6%). The *picrate*, orange needles (from ethanol), has m. p. 163—165° (Found: C, 62·1; H, 3·6. $C_{17}H_{12},C_6H_3O_7N_3$ requires C, 62·0; H, 3·4%), the 1 : 3 : 5-*trinitrobenzene* complex, canary-yellow needles (from ethanol), m. p. 187—189° (Found: C, 64·2; H, 3·6; N, 10·0. $C_{17}H_{12},C_6H_3O_6N_3$ requires C, 64·3; H, 3·5; N, 9·8%), and the 2 : 4 : 7-*trinitrofluorenone* complex, bright orange needles (from acetic acid), m. p. 186—187° (Found: C. 67·7; H, 3·0; N, 8·0. $C_{17}H_{12},C_{13}H_5O_7N_3$ requires C, 67·8; H, 3·2; N, 7·9%).

Michael Condensations by Use of Sodium Methoxide in Methanol and (A) *Vinyl Cyanides*, (B) *Alkyl Acrylates.*—(A) Methyl 9-2′-cyanoethylfluorene-9-carboxylate was prepared from methyl fluorene-9-carboxylate (1·12 g., 1 mol.), sodium (0·023 g., 0·2 atom), and vinyl cyanide (0·29 g., 1·1 mols.) in anhydrous methanol (2·5 ml.) as described for the methyl homologue (I) except that the cyano-ester did not crystallise from the reaction mixture after 24 hours. It was isolated in the usual way, and had m. p. 84—86° (1·04 g., 76%).

2-(9-Carbomethoxy-9-fluorenyl)propyl cyanide, prepared analogously from allyl cyanide (crotononitrile), had m. p. 72—75° (0·82 g., 57%). Loss in crystallisation accounts for the low yield. Hydrolysis and isolation of the carboxylic acids has repeatedly in this work given higher yields (see below).

(B) *Methyl* β-(9-*carbomethoxy*-9-*fluorenyl*)*propionate*. Methyl fluorene-9-carboxylate (1·12 g., 1 mol.), methanol (2·5 ml.), sodium (2·3 ml. of a solution of 0·23 g. of sodium in 23 ml. of methanol), and methyl acrylate (0·65 g., 1·5 mols.) (containing 0·1% of quinol) were left for 4 hours, then scratched. Crystals separated rapidly, and reaction was probably complete in 6 hours, but the mixture was invariably left overnight in a refrigerator to complete crystallisation. The main crop (1·25 g.) was pure. The filtrate, on being worked up as usual, gave a further crop (0·12 g.). This *diester* crystallised in thick rectangular plates (from methanol) (1·37 g., 88%), m. p. 68—69° (Found: C, 73·4; H. 5·7. $C_{19}H_{18}O_4$ requires C, 73·5; H, 5·8%). Hydrolysis of the diester (1·55 g.) by boiling it with 10N-potassium hydroxide (2 ml.) in 2-methoxyethanol (5 ml.) for 20 minutes, pouring the whole into water, and adding hydrochloric acid to the clear solution, gave β-9-fluorenylpropionic acid (1·07 g., 90%); on recrystallisation from methyl cyanide this had m. p. 145—147°, *i.e.*, higher than that of the acid prepared by hydrolysis of the cyanide (140—145°, A. Campbell and Tucker, *loc. cit.*; Wislicenus and Mocker, *Ber.*, 1913, **46**, 2789, gave 148—149°).

β-9-Fluorenylbutyric acid was prepared from methyl fluorene-9-carboxylate (1·12 g., 1 mol.), methyl crotonate (0·75 g., 1·5 mols.), and sodium (0·023 g., 0·2 atom) in methanol (5 ml.), which were left for 4 days at room temperature. Stellar clusters of crystals of dimethyl 9 : 9′-difluorenyl-9 : 9′-dicarboxylate, m. p. 237° (0·04 g., from acetic acid) (Found: C. 80·3; H, 5·2. Calc. for $C_{30}H_{22}O_4$: C, 80·7; H, 5·0%), were removed, and the filtrate was evaporated on the steam-bath in an air-blast. The residue was boiled with 10N-potassium hydroxide (2 ml.) and 2-methoxyethanol (5 ml.) for 15 minutes, and the solution poured into water, giving a milky suspension cleared when boiled with charcoal (0·5 hour). Hydrochloric acid gave β-9-fluorenylbutyric acid, m. p. 145° (0·74 g., 60%), which after crystallisation from methyl cyanide had m. p. 147—149°—again, higher than that of acid prepared from the cyanide (Tucker, *loc. cit.*, gives m. p. 143—147°). Ethyl esters gave somewhat lower yields. When in the above the original mixture was left for 3 weeks, the yield was slightly less and there was also isolated

(at the water-precipitation stage) fluorenol (0·13 g.). Fluorene failed to react with ethyl crotonate in presence of sodium ethoxide in ethanol even when the mixture was boiled for 3 days.

Thanks are due to Miss R. H. Kennaway and Mr. J. M. L. Cameron for micro-analyses, and to Mr. A. Campbell, B.Sc., for gifts of acrylic esters.

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147. *The Isomerisation of Aromatic Ketones through the Agency of Aluminium Chloride.*

By G. BADDELEY and A. G. PENDLETON.

The reaction between acetyldurene and excess of aluminium chloride at 100° provides a mixture of acetylprehnitene (80%), diacetyldurene (10%), and aromatic hydrocarbon (10%); 3 : 4 : 5-trimethylacetophenone (75%) and hexamethylbenzene (12%) were isolated from the products of interaction at 150°. At 100°, 9-acetyl-*s*-octahydroanthracene and 9-acetyl-*s*-octahydrophenanthrene afford 7-acetyl-2-methyl-4 : 5-*cyclo*hexenoindane (XVIII) in 75—80% yield. The mechanisms of the reactions are discussed.

o-ALKYLARYL ketones, in contrast to other alkylaryl ketones, become unstable at 80—150° in the presence of hydrogen halide and excess of aluminium halide and undergo a variety of irreversible changes which can be classified and illustrated as follows (*J.*, 1944, 232; 1950, 994): (i) The ketone may suffer fission into aromatic hydrocarbon and an acyl cation which recombine to provide an isomeric ketone (I ⟶ II). (ii) The *ortho*-alkyl group may migrate intramolecularly to the adjacent *meta*-position (III ⟶ IV). (iii) Migration of the acyl group may provide an isomeric *o*-alkylaryl ketone which isomerises to the corresponding *m*-alkylaryl ketone (V ⟶ VI). (iv) The *ortho*-alkyl group may migrate to the neighbouring *meta*-position when this is already occupied by an alkyl group; the more mobile alkyl group will then migrate to the *para*-position (VII and VIII ⟶ IX; Auwers, *Annalen*, 1928, **460**, 254). (v) In *oo'*-dialkylaryl ketones, both *ortho*-alkyl groups may migrate to the corresponding *meta*-positions (X ⟶ XI). In all instances, one molecular proportion of aluminium halide combines with the carbonyl group to form an oxonium complex, and additional aluminium halide is needed to effect isomerisation.

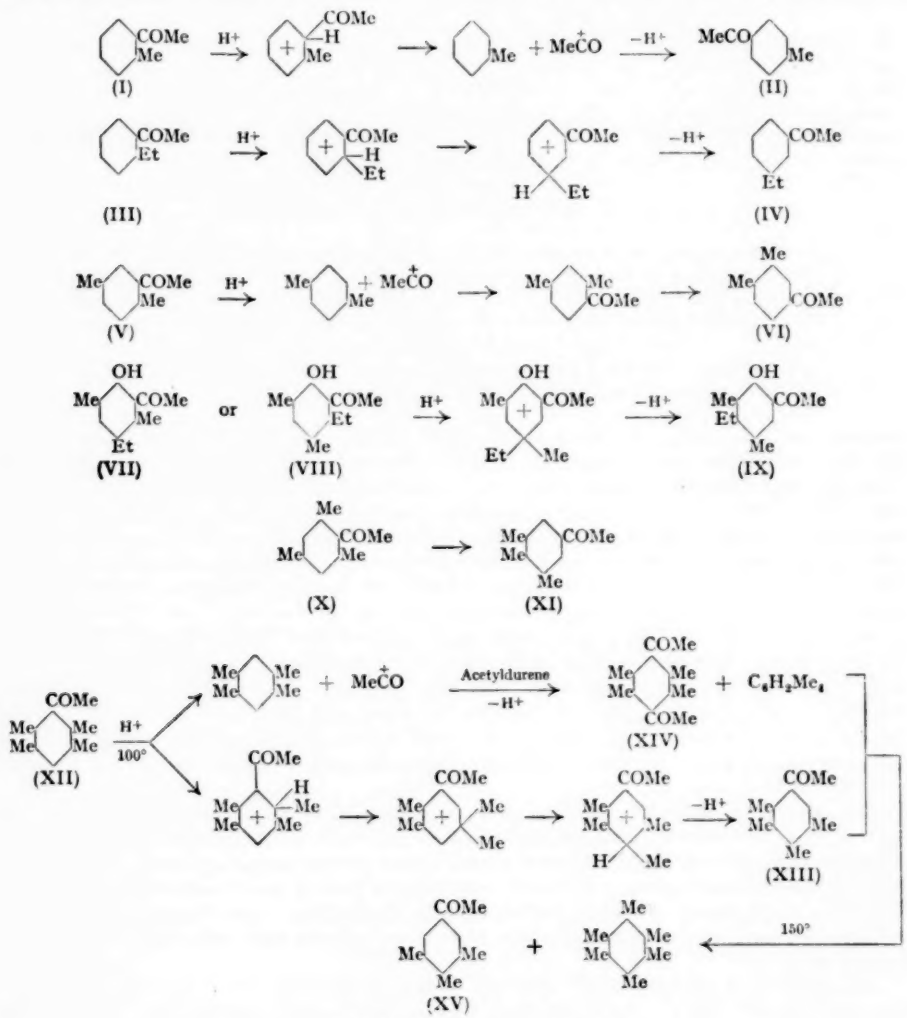
Up to the present, the aromatic ketones which have been isomerised through the agency of aluminium halide have contained two or more unsubstituted positions in the benzene ring and have provided ketones which have only hydrogen atoms in the positions *ortho* to the carbonyl group. We now report the action of aluminium chloride on three ketones, acetyldurene (2 : 3 : 5 : 6-tetramethylacetophenone) and 9-acetyl-*s*-octahydroanthrancene and -phenanthrene, which have only one nuclear position occupied by a hydrogen atom.

At 100°, acetyldurene (XII) afforded acetylprehnitene(2 : 3 : 4 : 5-tetramethylacetophenone) (XIII) (80%), diacetyldurene (XIV) (10%), and hydrocarbon (10%). The last two arise from fission of acetyldurene into durene and acetyl cation; as a consequence of steric inhibition of conjugation between acetyl group and benzene ring (*Nature*, 1939, **144**, 444; Meyer, *Ber.*, 1895, **28**, 3213; 1896, **29**, 848, 2564) acetyldurene readily affords diacetyldurene by acetylation. Acetylprehnitene, on the other hand, is the product of intramolecular displacement of one of the *o*-methyl groups.

5-Acetylhemimellitene (3 : 4 : 5-trimethylacetophenone) (XV) (75%) and hexamethylbenzene (12%) were isolated from the products of interaction at 150°; they arise from demethylation of acetylprehnitene by aromatic hydrocarbon, for this ketone in the absence

of aromatic hydrocarbon is unaffected by excess of aluminium chloride at 150°. The demethylation of *p*-cresol by aromatic hydrocarbon has been reported previously by one of us (*J.*, 1943, 527).

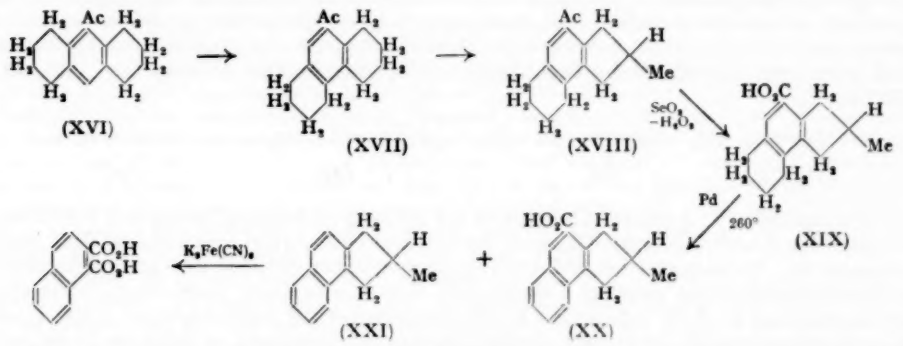
At 100°, 9-acetyl-*s*-octahydroanthracene (XVI) afforded an isomeric ketone; the following data show this to be 7-acetyl-2-methyl-4 : 5-*cyclo*hexenoindane (XVIII): (i) It readily provided a semicarbazone and therefore, unlike (XVI), has a carbonyl group which



(All the rings are aromatic.)

is not sterically hindered. (ii) It is a methyl ketone, as oxidation by selenium dioxide provided a glyoxal derivative which afforded an acid $C_{14}H_{17}\cdot CO_2H$ (XIX) in the presence of alkaline hydrogen peroxide. (iii) This acid evolved two molecular equivalents of hydrogen when heated with palladium at 260° and therefore has only one tetrahydrogenated aromatic ring; the other products of this reaction were an acid $C_{14}H_{13}\cdot CO_2H$ (XX) and a hydrocarbon $C_{14}H_{14}$ (XXI). (iv) The acid $C_{14}H_{17}\cdot CO_2H$ has one methyl group, as oxidation

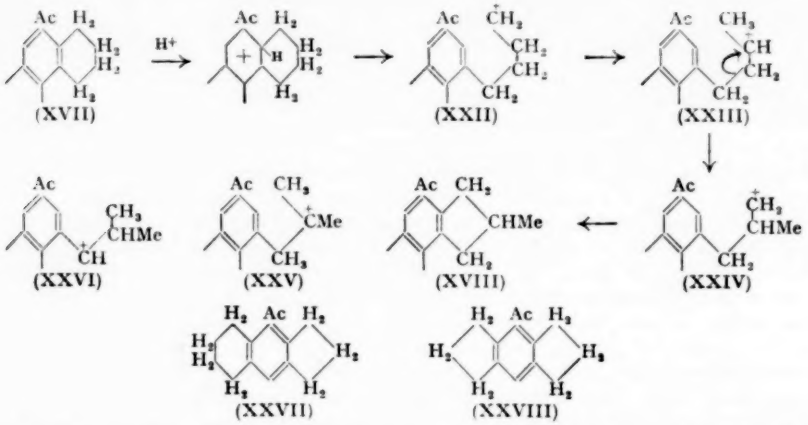
by chromic acid (Kuhn and Roth, *Ber.*, 1933, **66**, 1274) provided acetic acid (0·83 mol.). (v) The hydrocarbon $C_{14}H_{14}$ afforded naphthalene-1 : 2-dicarboxylic acid on oxidation with potassium ferricyanide and was thereby identified as 1-, 2- or 3-methyl-4 : 5-benzindane. (vi) These three hydrocarbons were synthesised. 1- and 2-Methyl-4 : 5-benzindane were obtained by Clemmensen reduction of 1- and 2-methyl-4 : 5-benzindan-3-one which, in turn, were prepared as described by Pfeiffer, Jenning, and Stöcker (*Annalen*, 1949, **563**, 73) and Cook, Dansi, Hewett, Iball, Mayneord, and Roe (*J.*, 1935, 1324) respectively. 3-Methyl-4 : 5-benzindane was obtained by addition of methylmagnesium iodide to 4 : 5-benzindan-3-one, derived from β-2-naphthylpropionic acid as described by Ansell and Hey (*J.*, 1950, 2874), and reduction of the resulting 3-methyl-4 : 5-benzindan-3-ol by hydriodic acid. We prepared β-2-naphthylpropionic acid from 2-naphthylmethyl bromide; our sample of 2-naphthylmethylmalonic acid melted at 147—148° (Found : C, 69·2; H, 4·9. Calc. for $C_{14}H_{12}O_4$: C, 68·9; H, 4·9%) and not at 94—95° as recorded by Meyer and Sieglitz (*Ber.*, 1922, **55**, 1835). These three methyl derivatives of 4 : 5-benzindane form crystalline complexes with picric acid and 1 : 3 : 5-trinitrobenzene; the melting points of these derivatives and those of 4 : 5-benzindane and the hydrocarbon $C_{14}H_{14}$ are assembled in the Table on p. 811; they clearly indicate that the last-mentioned is 2-methyl-4 : 5-benzindane and this was confirmed by mixed-melting-point determinations. (vii) 9-Acetyl-*s*-octahydrophenanthrene (XVII) provides the same isomeric ketone (XVIII) as does 9-acetyl-*s*-octahydroanthracene, whereas 6-acetyltetralin is unaffected by aluminium chloride at 100°; therefore, in 9-acetyl-*s*-octahydrophenanthrene, the tetrahydrogenated six-membered ring adjacent to the carbonyl group is the one which contracts to a five-membered ring and the product is 7-acetyl-2-methyl-4 : 5-*cyclo*hexenoindane (XVIII).



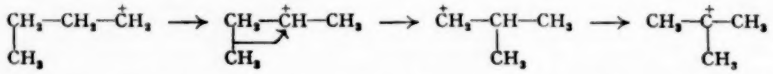
The isomerisation of 9-acetyl-*s*-octahydroanthracene to the corresponding phenanthrene derivative (XVI ⟶ XVII) is analogous to that of acetyldurene to acetylprehnitene. The isomerisation of 9-acetyl-*s*-octahydrophenanthrene to 7-acetyl-2-methyl-4 : 5-*cyclo*hexenoindane (XVII ⟶ XVIII) under conditions which do not affect acetylprehnitene was not unexpected as work in these laboratories has demonstrated that, in the interaction of aromatic ketones with aluminium halide, the methyl group is less mobile than are other alkyl groups; a possible explanation of this isomerisation arises from the observation,

made by Mr. Pickles in these laboratories, that whereas 2 : 5-dimethyl- and 2 : 5-diethylacetophenone rearrange to the corresponding 3 : 5-isomers, 2 : 5-di-*n*-propylacetophenone suffers considerable disproportionation into 3-*n*-propylacetophenone (35%) and more highly alkylated acetophenones; apparently, the 2-propyl group can be ejected as the propyl or *iso*propyl cation. Should the *cyclo*hexeno-group adjacent to the carbonyl group

in 9-acetyl-*s*-octahydrophenanthrene behave similarly, the following changes become possible:



The primary carbonium ion (XXII) rearranges to the secondary carbonium ion (XXIII) which, by a Wagner–Meerwein transformation, provides (XXIV). This cation, though less stable than either (XXV) or (XXVI), is the only one of these three which can provide ring closure; the product is (XVIII). The formation and rearrangement of (XXII), though speculative, have a precedent in the isomerisation of benzene homologues in the presence of aluminium halide; for example, a *n*-butyl group can provide a *sec.*-butyl group and the latter a *tert.*-butyl group; these rearrangements occur in the alkyl cation and have been formulated by Nightingale and Smith (*J. Amer. Chem. Soc.*, 1939, **61**, 101) as:



The instability of *o*-alkylaryl ketones in the presence of excess of aluminium halide is a consequence of steric interaction between the acyl and vicinal alkyl groups (*idem*, *ibid.*) and, undoubtedly, the isomerisation of 9-acetyl-*s*-octahydrophenanthrene to 7-acetyl-2-methyl-4 : 5-*cyclo*hexenoindane provides a decrease in this type of steric interaction. Evidence of the decrease in steric interaction which accompanies the replacement of a six- by a five-membered ring in compounds of this type has been obtained on previous occasions; for example, application of Raman spectra and interaction with methylmagnesium bromide and alkaline hypochlorite, respectively, have demonstrated that steric hindrance decreases in the series 9-acetyloctahydroanthracene > 4-acetyl-5 : 6-*cyclo*hexenoindane (XXVII) > 4-acetyl-*s*-hydrindacene (XXVIII) (Arnold and Rondestvedt, *ibid.*, 1946, **68**, 2176; 1945, **67**, 1265; Arnold and Craig, *ibid.*, 1948, **70**, 2791).

Experimental

Acetyldurene and Aluminium Chloride.—(a) *At* 100°. The ketone (7·5 g.), the chloride (15 g.), and sodium chloride (1 g.) were heated together for 2 hours; distillation of recovered organic material provided fractions (i), b. p. 90—120°/20 mm. (0·8 g.) and (ii) b. p. 130—140°/20 mm. (5·9 g.), and a residue (0·8 g.) which solidified on cooling and provided pure diacetyldurene (m. p. and mixed m. p. 178—179°) after recrystallisation from ethanol. Fraction (i) had the physical properties (b. p. 204°; m. p. −4°) of prehnitene but is probably a mixture of aromatic hydrocarbons as nitration by cold concentrated nitric–sulphuric acids provided a product, m. p. 152—162°, which was unaffected by recrystallisation; dinitroprehnitene melts at 178° (Jacobsen, *Ber.*, 1886, **19**, 1209; Smith and Cass, *J. Amer. Chem. Soc.*, 1932, **54**, 1614) and dinitrodurene at 205° (Nef, *Annalen*, 1887, **237**, 4). On a subsequent

occasion, this hydrocarbon fraction was found to contain hexamethylbenzene (m. p. and mixed m. p. 165—166°). Fraction (ii) was identified as acetylprehnitene [*semicarbazone*, m. p. and mixed m. p. 209° (Found: N, 18·5. $C_{13}H_{19}ON_3$ requires N, 18·0%)]; alkaline hypochlorite oxidised it to 2 : 3 : 4 : 5-tetramethylbenzoic acid (m. p. and mixed m. p. 165°).

(b) *At* 150°. A mixture of the ketone (7·5 g.), aluminium chloride (15 g.), and sodium chloride (1 g.) was fused at 100° and the orange-red melt heated at 150° for 3 hours. The recovered organic material, b. p. 135—140°/20 mm. (6·0 g.), was a mixture of oil (5·2 g.) and solid (0·8 g.) and was filtered. The solid crystallised from ethanol in colourless prisms, m. p. 165—166° (Found: C, 88·4; H, 11·1. Calc. for $C_{12}H_{18}$: C, 88·9; H, 11·1%). Jacobsen (*loc. cit.*) and Smith and Cass (*loc. cit.*) give m. p. 166° for hexamethylbenzene. The oil was identified as 3 : 4 : 5-trimethylacetophenone (semicarbazone, m. p. and mixed m. p. 217°). Subsequently, the hydrocarbon and ketonic components were separated by dissolving the mixture in light petroleum and extracting it with 80% sulphuric acid in which ketonic material is readily soluble.

Acetylprehnitene and Aluminium Chloride at 150°.—The ketone was recovered unchanged after 3 hours.

9-*Acetyl*-s-*octahydroanthracene and Aluminium Chloride.*—The ketone (50 g.), the chloride (76 g.) and sodium chloride (3 g.) were heated together at 100° for 2 hours. The organic product, b. p. 148°/0·12 mm. (45 g.), consisted of a solid, 7-*acetyl*-2-*methyl*-4 : 5-cyclo*hexenoindane* (see below) (30·2 g.), and an oil (14·8 g.) which were separated by filtration. The solid crystallised from ethanol in bundles of slender colourless needles, m. p. 97—98° (Found: C, 83·9; H, 8·7. $C_{16}H_{20}O$ requires C, 84·2; H, 8·8%). A sample of the oil (5·0 g.) was heated at 100° for 2 hours with aluminium chloride (8 g.) and sodium chloride (1 g.) and provided a further sample of the solid, m. p. 97—98° (1·5 g.), and oil (2·4 g.).

The solid formed a *semicarbazone* which crystallised from ethanol in needles, m. p. 154—155° (Found: N, 15·0. $C_{17}H_{23}ON_3$ requires N, 14·8%), and an *oxime* which crystallised from methanol in prisms, m. p. 154—155° (Found: N, 5·7. $C_{16}H_{21}ON$ requires N, 5·8%).

The solid (5 g.) was added to a stirred solution of selenium dioxide (2·5 g.) in water (0·5 c.c.) and dioxan (34 c.c.) at 55°, and the mixture was boiled under reflux for 4 hours. The precipitated selenium was separated by filtration and the filtrate cooled and diluted with water. The glyoxal derivative separated as a white solid, m. p. 107—112° (5·7 g.). A sample (4 g.) was dissolved in ethanol (60 c.c.) and aqueous hydrogen peroxide (30%; 20 c.c.), and 10% sodium hydroxide solution was added dropwise until reaction was complete. The resulting solution was warmed to 80° for 30 minutes, diluted with water, decolourised with animal charcoal, cooled, and acidified with concentrated hydrochloric acid. The precipitated 2-*methyl*-4 : 5-cyclo*hexenoindane*-7-*carboxylic acid* was separated, washed with water, dried, and recrystallised from ethanol. The acid (3·3 g.) melted at 207—208° [Found: C, 78·5; H, 7·9; Me (Kuhn–Roth), 5·4. $C_{15}H_{18}O_2$ requires C, 78·3; H, 7·8; 1Me, 6·5%].

This acid (5·0 g.) was heated with palladised charcoal (2 g.) at 260° in a slow stream of carbon dioxide. Hydrogen (922 c.c. Calc. for four atoms: 975 c.c.) was collected in 6 hours. The reaction mixture was cooled and extracted with ether and the extract washed with 2N-sodium hydroxide and dried (K_2CO_3). The alkaline washings were acidified and provided 2-*methyl*-4 : 5-*benzindane*-7-*carboxylic acid*, needles (0·7 g.), m. p. 230—232°, from ethanol (Found: C, 79·7; H, 6·2. $C_{15}H_{14}O_2$ requires C, 79·7; H, 6·2%). The ethereal extract provided 2-*methyl*-4 : 5-*benzindane* (2·0 g.), b. p. 127°/0·2 mm. (Found: C, 92·1; H, 7·9. $C_{14}H_{14}$ requires C, 92·3; H, 7·7%). This hydrocarbon formed a *picrate* and an addition *compound* with 1 : 3 : 5-trinitrobenzene, for which see the Table.

A mixture of the above hydrocarbon $C_{14}H_{14}$ (0·4 g.) and a solution of potassium ferricyanide (25 g.) and potassium hydroxide (4·3 g.) in water (90 c.c.) was vigorously stirred at 60° for

	Picrate			*s*-$C_6H_3(NO_2)_3$ compound		
		Found, %.[a]			Found, %.[b]	
Parent compound	M. p.	C	H	M. p.	C	H
4 : 5-Benzindane	109—110°[c]	—	—	119—120°	60·2	3·6
1-Methyl-4 : 5-benzindane	88—89	58·2	4·0	88—89	61·0	4·1
2-Methyl-4 : 5-benzindane	90·5—91[d]	—	—	103·5—104[e]	—	—
3-Methyl-4 : 5-benzindane	108—109	58·1	4·1	114—115	61·4	4·5
Hydrocarbon $C_{14}H_{14}$	90·5—91[d]	58·3	4·1	103·5—104[e]	61·1	4·1

[a] For the alkyl derivatives, $C_{20}H_{17}O_7N_3$ requires C, 58·4; H, 4·1%. [b] For 4 : 5-benzindane, $C_{19}H_{15}O_6N_3$ requires C, 59·8; H, 3·9%. For the alkyl derivatives, $C_{20}H_{17}O_6N_3$ requires C, 61·1; H, 4·3%. [c] Kruber (*Ber.*, 1932, **65**, 1388) records 110°. [d, e] No depression on admixture of pairs.

24 hours. Most of the oil had now disappeared and the remainder was removed with steam. The reaction mixture was cooled and filtered and the filtrate carefully acidified. The precipitate crystallised from acetic acid in slender colourless needles (0·2 g.), m. p. 166—167° (Found: C, 72·6; H, 3·0. Calc. for $C_{12}H_6O_3$: C, 72·7; H, 3·0%), and did not depress the m. p. [166—167°; Kruber (*loc. cit.*) gives m. p. 163—164°] of naphthalene-1 : 2-dicarboxylic anhydride obtained from **4** : 5-benzindane by the above procedure.

3-*Methyl*-**4** : 5-*benzindane.*—**4** : 5-Benzindan-3-one (4 g.) in ether was gradually added to a solution of magnesium (1·35 g.) in methyl iodide (6·25 g.) and ether (50 c.c.). After being kept overnight, the mixture was poured on ice and acidified with ammonium chloride and a little dilute sulphuric acid. The ethereal extract was washed with sodium carbonate solution, then dried (K_2CO_3), and the ether removed at room temperature under reduced pressure. The crystalline residue of 3-*methyl*-**4** : 5-*benzindan*-3-*ol* crystallised from ether in small colourless prisms (4·2 g.), m. p. 117—118° (Found: C, 84·3; H, 7·4. $C_{14}H_{14}O$ requires C, 84·8; H, 7·1%). A mixture of the alcohol (3·25 g.), hydriodic acid (10 c.c.; *d* 1·7), and red phosphorus (1 g.) was boiled under reflux in an atmosphere of nitrogen for 3 hours; it was then diluted with water and extracted with ether, the ethereal extract filtered and washed with sodium thiosulphate solution, and the ether removed. The residue was distilled with steam and provided 3-methyl-**4** : 5-benzindane (0·8 g.).

2-*Methyl*-**4** : 5-*benzindane.*—This hydrocarbon (2·7 g.) was obtained by Clemmensen reduction of 2-methyl-**4** : 5-benzindan-3-one (5·2 g.).

1-*Methyl*-**4** : 5-*benzindane.*—This (0·85 g.) was obtained by Clemmensen reduction of 1-methyl-**4** : 5-benzindan-3-one (1·75 g.).

The *picrates* and the addition *compounds* with **1** : **3** : 5-trinitrobenzene of the three isomers crystallised from ethanol (see Table). **4** : 5-Benzindane gave an addition *compound* with **1** : **3** : 5-trinitrobenzene (see Table).

9-*Acetyl*-s-*octahydrophenanthrene and Aluminium Chloride.*—These components (5 g. and 8 g. respectively) and sodium chloride (1 g.) were fused together at 100° for 2 hours and provided 7-acetyl-2-methyl-**4** : 5-benzindane (2·7 g.), m. p. and mixed m. p. 97—98°, and an oil (0·9 g.), b. p. 160°/0·5 mm.

6-*Acetyltetrahydronaphthalene and Aluminium Chloride.*—These components (9 g. and 18 g. respectively) and sodium chloride (1 g.) were fused together at 100° for 2 hours. The ketone (7·5 g.), b. p. 150°/15 mm. (oxime, m. p. and mixed m. p. 106—107°), was recovered unchanged. The oxime separated from ethanol in crystals, m. p. 85°, and reverted to crystals, m. p. 106—107°, on storage.

We are indebted to Professor J. W. Cook, F.R.S., and to Imperial Chemical Industries Limited, Dyestuffs Division, for gifts of *s*-octahydrophenanthrene and *s*-octahydroanthracene respectively, and to Mr. R. Williamson for valuable help in the study of the isomerisation of acetyldurene.

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148. *The Different Reaction Velocities of Enantiomers with a Common Optically Active Reagent. Part II.* Reactions between Stereoisomeric Menthols and Menthyl* iso*Cyanates.*

By JOHN READ and DAVID S. P. ROEBUCK.

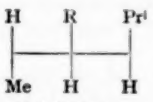
*iso*Cyanates (carbimides) derived from (−)-, (±)-, (+)-*neo*-, and (+)-*iso*-menthylamine have been prepared and brought into reaction with the three corresponding types of menthols. The resulting pure menthyl menthylcarbamates have been characterised and applied in studying a series of competitive reactions leading to the formation of mixtures of pairs of these compounds. Two new virtual optical resolutions of (±)-menthol and a partial optical resolution of (±)-*iso*menthol are described.

THE present investigation differs in two important respects from that reported in Part I * of this series. First, the stereoisomers now described as reacting with a common optically active reagent were not always enantiomers; secondly, the experiments utilised a series

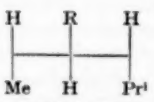
* Part I, *J.*, 1936, 1219.

of reactants having varied but closely similar molecular configurations. The menthyl *iso*cyanates (R = NCO) and menthols (R = OH) concerned all belonged to the (−)-, (+)-*neo*-, and (+)-*iso*-series, possessing the following relative configurations (Read and Grubb, *J.*, 1934, 1781) :

(I) (−)-



(II) (+)-*neo*-



(III) (+)-*iso*-

In a series of reactions between an equimolecular mixture of two stereoisomers, present in excess (3 mols.), and an individual optically active reagent (1 mol.), the product was always a pair of stereoisomeric menthyl menthylcarbamates, formed in a bimolecular reaction (Pickard, Littlebury, and Neville, *J.*, 1906, **89**, 93), and usually produced in different amounts. The optical rotatory power of each pure constituent being known, it was possible to calculate the quantitative composition of the mixture from its observed optical rotation. Some stereoisomeric preferences of considerable interest were established in the series of nine experiments which are summarised in the following table :

Results of competitive reactions between various menthols and menthyl isocyanates.

Reactants	Predominating ester (%)	Ratio of the two esters
(1) (±)-Menthol (3 mols.); (−)-menthyl *iso*cyanate (1 mol.)	(+)-Menthyl (62·3)	1·7 : 1
(2) (±)-Menthol (3 mols.); (+)-*neo*menthyl *iso*cyanate (1 mol.)	(−)-Menthyl (76·9)	3·3 : 1
(3) (±)-Menthol (3 mols.); (+)-*iso*menthyl *iso*cyanate (1 mol.)	(+)-Menthyl (50·8)	1·1 : 1
(4) (±)-*neo*Menthol (3 mols.); (−)-menthyl *iso*cyanate (1 mol.)	(+)-*neo*Menthyl (50·2)	1·1 : 1
(5) (±)-*iso*Menthol (3 mols.); (−)-menthyl *iso*cyanate (1 mol.)	(−)-*iso*Menthyl (75·0)	3·0 : 1
(6) (−)-Menthol (1·5 mols.), (+)-*neo*menthol (1·5 mols.); (−)-menthyl *iso*cyanate (1 mol.)	(−)-Menthyl (69·3)	2·3 : 1
(7) (−)-Menthol (1·5 mols.), (+)-*iso*menthol (1·5 mols.); (−)-menthyl *iso*cyanate (1 mol.)	(+)-*iso*Menthyl (50·9)	1·1 : 1
(8) (−)-Menthol (1 mol.); (−)-menthyl *iso*cyanate (1·5 mols.), (+)-*neo*menthyl *iso*cyanate (1·5 mols.)	(−)-Menthylcarbamate (63·9)	1·8 : 1
(9) (−)-Menthol (1 mol.); (−)-menthyl *iso*cyanate (1·5 mols.), (+)-*iso*menthyl *iso*cyanate (1·5 mols.)	(+)-*iso*Menthylcarbamate (65·7)	2·0 : 1

Experiment (1) illustrates the pronounced tendency of an asymmetric reacting molecule or radical to show a preference for its enantiomeric rather than its coincident form; a comparative neglect of the coincident form is shown also in (9). (−)-Menthyl (−)-menthylcarbamate is formed with the greater alacrity only in two experiments (6 and 8) in which the production of the second (*neo*menthyl) ester is retarded by the presence of a *cis-iso*propyl radical (see II, above).

In the first four experiments the diastereoisomer of higher melting point is invariably formed in greater amount, denoting a higher reaction velocity; this is most likely the case in (5) also, but in this instance the melting point of (+)-*iso*menthyl (−)-menthylcarbamate is at present unknown. As a similar example in another series, Read and Grubb (*J. Soc. Chem. Ind.*, 1932, **51**, 329T) found that (+)-menthol reacted more rapidly than (−)-menthol with (−)-menthoxyacetyl chloride, and that the (+)-menthyl ester had the higher melting point. Again, (+)-menthyl (−)-menthylglycine, with its two enantiomeric menthyl radicals, has a higher melting point than (−)-menthyl (−)-menthylglycine (Clark and Read, *J.*, 1934, 1776), and would probably be the predominating product of a reaction between (−)-menthylamine and an excess of (±)-menthyl chloroacetate.

These observations afford at any rate a partial answer to two queries raised by Galloway and Read (*loc. cit.*, p. 1220) : (1) it has proved possible " to adduce a sustained and connected series of reactions throughout which a common molecule or radical " shows a preference in each instance for its enantiomeric form; and (2) " the relative rates of formation of the two diastereoisomeric products " of a considerable variety of reactions have been correlated to some extent " with the comparative physical properties of the two substances." In the last four of the nine experiments listed above the two products are not truly diastereoisomeric, and the relationships in question do not hold.

In view of the strong preference shown by (−)- [as against (+)-] menthol for (+)-*neo*menthyl *iso*cyanate in (2), the formation of a correspondingly large excess of (+)-*neo*-menthyl (−)-menthylcarbamate might have been expected in (4); in this case, however, the two esters are produced in practically equal amounts. A similar example is provided in (5) and (3). The order of allocation of the two reactive groups (−OH and −NCO) to the two stereoisomeric radicals concerned is therefore an important factor in determining the relative velocities of reaction.

A comparison of experiments (1) and (5) shows that (−)-menthyl *iso*cyanate prefers to react with (+)- [rather than (−)-] menthol, and with (−)-*iso*- [rather than (+)-*iso*-] menthol. A supplementary experiment (7) shows further that this reagent has a practically equal tendency to react with (−)-menthol and (+)-*iso*menthol.

It is clear from such considerations that experiments of this kind could be extended with profit in many directions. One related matter that has been explored in the present investigation is the bearing of such reactions upon the resolution of externally compensated menthols into their optically active components. That such an optical resolution is possible by a static method, depending upon fractional crystallisation of an equimolecular mixture of diastereoisomeric carbamates, is shown by the work of Pickard and his collaborators, who resolved (±)-1-*p*-hydroxyphenyl-2-phenylethane and (±)-*ac*-tetrahydro-2-naphthol (*J.*, 1906, **89**, 467, 1254) by fractionally crystallising the (−)-menthylcarbamates. As shown below, the mixture of esters obtained in experiments (1) and (2) above readily yielded pure (+)-menthyl (−)-menthylcarbamate and (−)-menthyl (+)-*neo*-menthylcarbamate respectively when fractionally crystallised; so far, however, it has not proved possible to detach the pure (+)- and (−)-menthol by hydrolysis, owing to the great stability of these esters.

As shown above, in experiment (5), (−)-*iso*menthol reacts much more rapidly than (+)-*iso*menthol with (−)-menthyl *iso*cyanate: a dynamic method of optical resolution should therefore be possible in which the chemical reaction becomes the effective resolving agent. In a first operation of this kind, the residual specimen of *iso*menthol contained 67% of the (+)-form, from which it is clear that pure (+)-*iso*menthol could be obtained by repeating the operation a number of times. In working practice it should be possible to prepare pure (+)-*iso*menthol by fractionally crystallising a mixture obtained from (±)-*iso*menthol by this method and containing a relatively small amount of (−)-*iso*-menthol, since (+)-*iso*menthol (m. p. 82·5°) is less soluble than (±)-*iso*menthol (m. p. 53·5°). Up to the present the optical resolution of (±)-*iso*menthol has not been accomplished and therefore the possibility now indicated has a particular interest.

Experimental

Preparation and Characterisation of Menthyl iso*Cyanates.*—(−)-*Menthyl* iso*cyanate.* Ethyl (−)-menthylcarbamate, prepared from (−)-menthylamine, ethyl chloroformate, and sodium hydrogen carbonate, by Neville and Pickard's method (*J.*, 1904, **85**, 688), had b. p. 112—115°/0·4 mm., m. p. 54·5—55·5°, $[\alpha]_D^{18}$ −83·6° (*c*, 0·9 in ethanol); when distilled with phosphoric oxide at 15—30 mm. it yielded (−)-menthyl *iso*cyanate, b. p. 98—100°/15 mm., $[\alpha]_D^{17}$ −55·01° (1 dm., homogeneous).

(±)-*Menthyl* iso*cyanate.* *Ethyl* (±)-*menthylcarbamate*, prepared from (±)-menthylamine [obtained from (±)-menthol, *via* (±)-menthone and (±)-menthone oxime], formed stout prisms, m. p. 93—94°, from aqueous alcohol (Found: N, 6·3. $C_{13}H_{25}O_2N$ requires N, 6·2%). (±)-*Menthyl* iso*cyanate*, prepared similarly to the (−)-compound, was a mobile oil, b. p. 120—123°/16 mm. (Found: N, 7·9. $C_{11}H_{19}ON$ requires N, 7·7%).

(+)-neo*Menthyl* iso*cyanate.* *Ethyl* (+)-neo*menthylcarbamate*, prepared in the usual way from (+)-*neo*menthylamine, crystallised from aqueous alcohol in large transparent prisms, m. p. 49·5—50°, $[\alpha]_D^{17}$ +46·5° (*c*, 1·8 in ethanol) (Found: N, 6·2%). (+)-neo*Menthyl* iso*cyanate* formed a mobile oil, b. p. 108—110°/16—17 mm., $[\alpha]_D^{14}$ −29·86° (1 dm., homogeneous) (Found: N, 7·8%).

(+)-iso*Menthyl* iso*cyanate.* *Ethyl* (+)-iso*menthylcarbamate*, prepared from (+)-*iso*menthylamine, formed a viscid oil; this crystallised readily in a mixture of snow and salt, but reverted to a thick fluid at room temperature, $[\alpha]_D^{17}$ +38·4° (*c*, 1·5 in ethanol) (Found: N, 6·4%).

(+)-iso*Menthyl* iso*cyanate* had b. p. 116—117°/35 mm., α_D^{16} +26·20° (1 dm., homogeneous) (Found: N, 7·9%).

Pure Menthyl Esters of Menthylcarbamic Acids.—(−)-*Menthyl* (−)-*menthylcarbamate.* An equimolecular mixture of (−)-menthol and (−)-menthyl *iso*cyanate was heated for 10 hours on a boiling-water bath. The product was steam-distilled, and the residue extracted with ether. Upon removal of ether from the dried extract, (−)-*menthyl* (−)-*menthylcarbamate* remained as a viscid oil which soon crystallised. Recrystallisation from light petroleum yielded small needles, m. p. 110—110·5°, $[\alpha]_D^{17}$ −94·2° (*c*, 1·1 in ethanol) (Found: C, 74·5; H, 11·7. $C_{21}H_{39}O_2N$ requires C, 74·8; H, 11·6%). (+)-*Menthyl* (−)-*menthylcarbamate*, prepared similarly from (+)-menthol, separated from light petroleum in transparent needles up to 2·5 cm. long, m. p. 120—121°, $[\alpha]_D^{18}$ −5·0° (*c*, 0·75 in ethanol) (Found: C, 74·4; H, 11·7%). (±)-*Menthyl* (−)-*menthylcarbamate*, prepared from (±)-menthol, formed small needles, m. p. 73—75°, $[\alpha]_D^{17}$ −50·8° (*c*, 1·2 in ethanol). The mean value of $[\alpha]_D$ for the pure (+)- and (−)-components of this ester is −49·6°. (−)-Menthyl (±)-menthylcarbamate was obtained from (−)-menthol and (±)-menthyl *iso*cyanate as a crystalline mass, m. p. 97—98°, $[\alpha]_D^{15}$ −43·3° (*c*, 2·1 in ethanol). The mean value of $[\alpha]_D$ for the esters of (+)- and (−)-menthylcarbamic acid with (−)-menthol (above) is −44·6°. (+)-neo*Menthyl* (−)-*menthylcarbamate*, prepared in the usual way, formed small needles, m. p. 121—122°, $[\alpha]_D^{17}$ −35·8° (*c*, 1·1 in ethanol) (Found: C, 73·8; H, 11·5%). (−)-neo*Menthyl* (−)-*menthylcarbamate* formed minute needles, m. p. 107—108°, $[\alpha]_D$ −62·9° (*c*, 1·6 in ethanol) (Found: C, 74·7; H, 11·6%). (+)-iso*Menthyl* (−)-*menthylcarbamate* separated from ethanol in small prisms, m. p. 84—85°, $[\alpha]_D^{19}$ −27·0° (*c*, 0·9 in ethanol) (Found: C, 74·9; H, 11·6%). (±)-*iso*Menthyl (−)-menthylcarbamate formed an amorphous solid mass, m. p. 73—74°, $[\alpha]_D^{16}$ −37·8° (*c*, 0·7 in ethanol). From these observations the calculated value $[\alpha]_D$ −48·6° is obtained for (−)-*iso*menthyl (−)-menthylcarbamate.

(−)-*Menthyl* (+)-neo*menthylcarbamate* was prepared from (−)-menthol and (+)-*neo*menthyl *iso*cyanate in the usual way, except that the heating was continued for 40 hours. The compound crystallised from ethanol in fine needles up to 2·5 cm. long, m. p. 114—115°, $[\alpha]_D^{18}$ −9·1° (*c*, 1·1 in ethanol) (Found: C, 74·7; H, 11·6%). (+)-*Menthyl* (+)-neo*menthylcarbamate*, prepared similarly, separated from ethanol in small transparent plates containing combined ethanol (2 mols.), m. p. 74·5—75·5°, $[\alpha]_D^{14}$ +85·0° (*c*, 1·4 in ethanol) (Found: C, 71·3; H, 11·3. $C_{21}H_{39}O_2N,2C_2H_6O$ requires C, 70·6; H, 11·1%).

(−)-*Menthyl* (+)-iso*menthylcarbamate* was obtained by heating an equimolecular mixture of (−)-menthol and (+)-*iso*menthyl *iso*cyanate at 100° for 12 hours, in the usual way. It formed transparent needles from ethanol, having m. p. 79—80°, $[\alpha]_D^{18}$ −24·6° (*c*, 0·7 in ethanol) (Found: C, 74·8; H, 11·3%). (+)-*Menthyl* (+)-iso*menthylcarbamate* had m. p. 82—83°, $[\alpha]_D^{17}$ +64·7° (*c*, 0·7 in ethanol) (Found: C, 74·5; H, 11·3%).

Competitive Reactions.—In all the following experiments an equimolecular mixture of two stereoisomerides (3 mols.) was brought into reaction with an individual optically active reagent (1 mol.), under the conditions specified for the first experiment. All the optical rotatory powers quoted were measured in absolute ethyl alcoholic solution (*c*, 1—3).

(1) (±)-*Menthol* (3 *mols.*) *and* (−)-*menthyl* iso*cyanate* (1 *mol.*). (±)-Menthol (23 g.) was heated on a boiling-water bath in a small flask fitted with reflux condenser and dropping funnel, each of which was closed with a calcium chloride tube. (−)-Menthyl *iso*cyanate (8·75 g.) was admitted gradually through the dropping funnel (2 hours), local concentration being avoided by vigorous shaking. After 12 hours' further heating the excess of menthol was removed by steam-distillation, the residual mixture of diastereoisomeric esters being then extracted with ether, the extract dried, and the solvent removed. The mixed esters weighed 13·92 g. and had $[\alpha]_D^{19·5}$ −38·6°, corresponding to 62·3% of (+)-menthyl ester and 37·7% of (−)-menthyl ester. The recovered menthol had $[\alpha]_D^{19·5}$ −2·0°, showing that partial optical resolution of the (±)-menthol had occurred as a result of the more rapid reaction of (+)-menthol.

(2) (±)-*Menthol* (3 *mols.*) *and* (+)-neo*menthyl* iso*cyanate* (1 *mol.*). In this experiment the heating was prolonged to 70 hours. The value, $[\alpha]_D^{14}$ +26·6° (0·8801 g. made up to 50 c.c. gave α_D^{14} +1·87° in a 4-dm. tube), indicated the presence of 76·9% of (−)- and 23·1% of (+)-menthyl ester. The unchanged menthol had $[\alpha]_D^{14}$ +0·2°.

(3) (±)-*Menthol* (3 *mols.*) *and* (+)-iso*menthyl* iso*cyanate* (1 mol.). The ester mixture obtained after 12 hours' heating had $[\alpha]_D^{15}$ +20·8°, and the unchanged menthol showed no measurable optical activity under the usual conditions. The calculated proportion of the (+)- ester is 50·8%, and of the (−)-menthyl ester 49·2%.

(4) (±)-neo*Menthol* (3 *mols.*) *and* (−)-*menthyl* iso*cyanate* (1 *mol.*). After 15 hours' heating

under the usual conditions the mixture of esters had $[\alpha]_D$ −49·3°, and the unchanged *neo*-menthol showed no measurable optical activity. The calculated proportions are 50·2% of the (+)- and 49·8% of the (−)-*neo*menthyl ester.

(5) (±)-iso*Menthol* (3 *mols.*) *and* (−)-*menthyl* iso*cyanate* (1 *mol.*). The mixed esters resulting after 10 hours' heating crystallised when kept *in vacuo* for a short time, and had $[\alpha]_D$ −43·2°, corresponding to 75·0% of the (−)- and 25·0% of the (+)-*iso*menthyl ester. The unchanged *iso*menthol was dextrorotatory.

(6) (−)-*Menthol* (1·5 *mols.*), (+)-neo*menthol* (1·5 *mols.*), *and* (−)-*menthyl* iso*cyanate* (1 *mol.*). (−)-Menthyl *iso*cyanate was added gradually to a mixture of (−)-menthol and (+)-*neo*menthol, and after 12 hours' heating the mixture of esters was isolated in the usual way. This product was an oil which readily solidified to an amorphous mass, having $[\alpha]_D^{17}$ −76·3°, corresponding to 69·3% of (−)-menthyl ester and 30·7% of (+)-*neo*menthyl ester.

(7) (−)-*Menthol* (1·5 *mols.*), (+)-iso*menthol* (1·5 *mols.*), *and* (−)-*menthyl* iso*cyanate* (1 *mol.*). The heating was continued for 10 hours, and the mixture of esters, which crystallised readily, had $[\alpha]_D^{15}$ −60·0°, corresponding to 50·9% of (+)-*iso*menthyl ester and 49·1% of (−)-menthyl ester.

(8) (−)-*Menthyl* iso*cyanate* (1·5 *mols.*), (+)-neo*menthyl* iso*cyanate* (1·5 *mols.*), *and* (−)-*menthol* (1 *mol.*). In this experiment the (−)-menthol was added progressively to the mixture of *iso*cyanates, and the heating was maintained for 25 hours. After steam-distillation the residual mixture of esters was obtained as a viscid syrup, $[\alpha]_D^{16}$ −63·5°, corresponding to 63·9% of (−)-menthyl (−)-menthylcarbamate and 36·1% of (−)-menthyl (+)-*neo*menthylcarbamate.

(9) (−)-*Menthyl* iso*cyanate* (1·5 *mols.*), (+)-iso*menthyl* iso*cyanate* (1·5 *mols.*), and (−)-*menthol* (1 *mol.*). A similar procedure with these three compounds yielded a mixture of esters having $[\alpha]_D^{18}$ −48·5°, which therefore consisted of 65·7% of (−)-menthyl (+)-*iso*menthylcarbamate and 34·3% of (−)-menthyl (−)-menthylcarbamate.

Experiments on the Optical Resolution of Externally Compensated Menthols.—Virtual resolution of (±)-*menthol with* (−)-*menthyl* iso*cyanate.* The mixture of esters from experiment (1) in the preceding section, containing 62·3% of (+)-menthyl (−)-menthylcarbamate, was crystallised from aqueous alcohol. The product (m. p. 90—91°) after three recrystallisations from absolute ethanol gave pure (+)-menthyl (−)-menthylcarbamate, m. p. 120—121°, $[\alpha]_D$ −5·0° (*c*, 0·75 in ethanol).

Virtual resolution of (±)-*menthol with* (+)-neo*menthyl* iso*cyanate.* The mixture of esters from experiment (2) above, containing 76·9% of (−)-menthyl (+)-*neo*menthylcarbamate, was subjected to fractional crystallisation from aqueous alcohol. After three crystallisations pure (−)-menthyl (+)-*neo*menthylcarbamate was obtained, m. p. 114·5—115·5°, $[\alpha]_D^{15}$ −9·2° (*c*, 1·5 in ethanol).

In neither of these two instances was it possible to liberate the free optically active menthol, since the carbamates resisted hydrolysis with alcoholic potassium hydroxide, 20% sulphuric acid, and other reagents; concentrated sulphuric acid broke down the esters, giving rise to menthene. It is of interest that (−)-menthyl phenylcarbamate (m. p. 104—105°, $[\alpha]_D^{19}$ −91·7°) yielded to hydrolysis with 2% alcoholic potassium hydroxide, giving (−)-menthol and aniline.

Partial Resolution of (±)-iso*Menthol with* (−)-*Menthyl* iso*Cyanate.*—(−)-Menthyl iso*cyanate* (2·23 g., 1 mol.) was brought into reaction with (±)-*iso*menthol (3·84 g., 2 mols.) in the usual way. After 10 hours' heating on a boiling-water bath, the excess of *iso*menthol was removed by steam-distillation followed by extraction with ether. The product (1·9 g.) had $[\alpha]_D^{18}$ +8·9° (0·6776 g. made up to 50 c.c. in ethanol gave α_D^{18} +0·48° in a 4-dm. tube), and thus contained about 67% of (+)-*iso*menthol and 33% of (−)-*iso*menthol.

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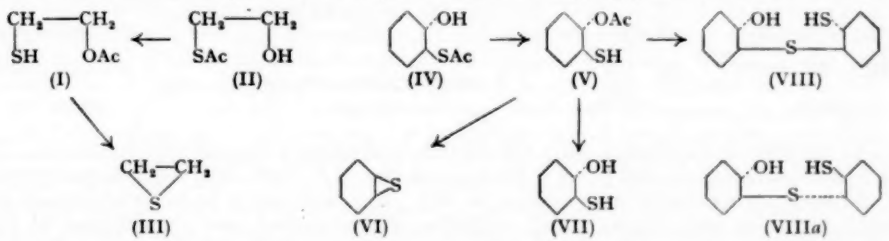
149. *Dithiols. Part XII.* The Alkaline Hydrolysis of Acetylated Hydroxy-thiols: A New Reaction for the Formation of Cyclic Sulphides.*

By L. W. C. Miles and L. N. Owen.

Deacetylation, with dilute aqueous alkali, of either the *O*- or the *S*-acetyl derivative of 2-mercaptoethanol leads to the formation of ethylene sulphide and polymeric material. *cyclo*Hexene sulphide is obtained in good yield by deacetylation of the *O*- or *S*-acetyl derivative of *trans*-2-mercapto*cyclo*hexanol with hot aqueous sodium carbonate; under more vigorous conditions the sulphide undergoes further reactions. Anomalous results reported earlier in the alkaline deacetylation of triacetyl 2 : 3-dimercaptopropanol (triacetyl BAL) have been fully explained; the initial product is 3-acetylthiopropylene sulphide, which under mild conditions can be isolated (yield 80%), but otherwise reacts further to give 3-hydroxy-2 : 2′ : 3′-trimercaptodipropyl sulphide and more complex products. 3-Acetylthiopropylene sulphide is also formed from the di-*S*-acetyl derivative of 2 : 3-dimercaptopropanol, whilst 2 : 3-dimercaptopropyl acetate gives 3-mercaptopropylene sulphide. The *O*- and di-*S*-acetyl derivatives of 3 : 4-dimercaptobutanol give 3-mercaptothiophan, the ring structure of which is proved by partial desulphurisation to thiophan. Cyclisation does not occur on alkaline deacetylation of the *O*- or the *S*-acetyl derivative of 2-hydroxy-2′-mercaptodiethyl sulphide. The formation of cyclic sulphides occurs through intramolecular elimination of acetic acid, and involves ester fission of the *O*-alkyl type.

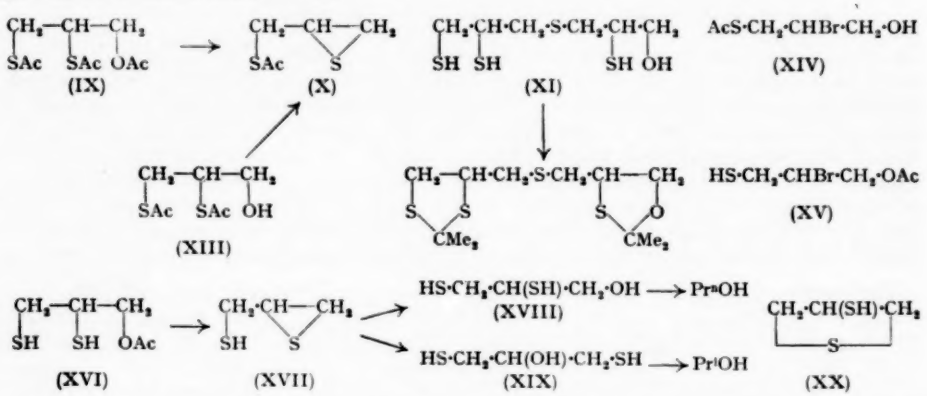
During studies carried out in these laboratories on the synthesis and reactions of dithiols, it has been observed that the deacetylation of acetylated hydroxy-thiols frequently proceeds abnormally, in that the thiol value of the hydrolysed material does not attain the theoretical (see, *e.g.*, Evans and Owen, *J.*, 1949, 244). In this connection the observation of Pavlic, Lazier, and Signaigo (*J. Org. Chem.*, 1949, **14**, 59), that 2 : 3-dimercaptopropyl acetate is rapidly hydrolysed in aqueous solution, is of interest, because it indicates that the presence of thiol groups can greatly increase the reactivity of a neighbouring acetyl group. As a first step in the investigation of these possibly related phenomena, it seemed desirable to find to what extent the presence of only one vicinal thiol group produced the same effects.



2-Mercaptoethyl acetate (I) has been obtained (Nylen and Olsen, *Svensk Kem. Tidsk.*, 1941, **53**, 274) by rearrangement of the isomeric thiolacetate (II) by heating it in aqueous solution; clearly, therefore, (I) is more stable than 2 : 3-dimercaptopropyl acetate. It has now been prepared by direct acetylation of 2-mercaptoethanol, following the method of Pavlic, Lazier, and Signaigo (*loc. cit.*), and although it was not decomposed in neutral solution it was rapidly hydrolysed in the presence of a small excess of cold dilute alkali to give ethylene sulphide (III) and much polymer. Nylen and Olsen (*loc. cit.*) reported the formation of polymer in the reaction of alkali with the isomer (II), and considered it to have been derived from the free hydroxy-thiol, but this explanation is untenable since 2-mercaptoethanol is stable in alkaline solution. There can be little doubt that the polymer is formed from ethylene sulphide and that the latter is an initial product of the deacetylation.

* Part XI, Owen and Smith, *J.*, 1951, 2973.

The corresponding *cyclo*hexane compounds were chosen for further investigation of the reaction, because of the greater stability and ease of isolation of *cyclo*hexene sulphide (cf. Culvenor, Davies, and Pausacker, *J.*, 1946, 1050). The addition of thiolacetic acid to *cyclo*hexene oxide took place readily at room temperature to give *trans*-2-acetylthio*cyclo*hexanol (IV) in good yield. This was stable to heat when pure, but at 100° in the presence of 1% of acetic acid it rearranged to the *O*-acetate (V) (cf. Sjöberg, *Ber.*, 1941, **74**, 64), which had earlier been obtained in poor yield by the addition of acetic acid to *cyclo*hexene sulphide (Culvenor, Davies, and Heath, *J.*, 1949, 282). By hydrolysis of the *O*-acetate with sodium hydroxide in aqueous alcohol there were obtained a trace of *cyclo*hexene sulphide (VI), *trans*-2-mercapto*cyclo*hexanol (VII), 2-hydroxy-2′-mercaptodi*cyclo*hexyl sulphide (VIII), and some polymer. However, when either (IV) or (V) was "steam-distilled" with aqueous sodium carbonate at 60° under reduced pressure, *cyclo*hexene sulphide was obtained in 70% yield from the distillate. The primary product of the deacetylation was therefore *cyclo*hexene sulphide, which under the more vigorous conditions of the earlier experiment had undergone ring-fission and had been largely converted into (VII), (VIII), and polymers. It may be observed that (VIII), formed by interaction of (VI) and (VII), although possessing a *trans*-configuration at each *cyclo*hexane ring (on the assumption that the usual Walden inversion occurs when the sulphide ring is opened) can nevertheless exist in two stereoisomeric forms, (VIII) and (VIII*a*) (cf. Owen and Smith, *J.*, 1951, 2973). It was obtained as a liquid, but it gave a crystalline 2 : 4-dinitrophenyl derivative which appeared to be homogeneous, and no indication was obtained of the presence of another stereoisomer.



In the light of the above results, the alkaline hydrolysis of the triacetyl derivative (IX) of 2 : 3-dimercaptopropanol (Evans, Fraser, and Owen, *J.*, 1949, 248) was re-investigated. 2 : 3-Dimercaptopropanol was obtained in 35% yield, and shown to be homogeneous by desulphurisation with Raney nickel, oxidation of the product, and identification of the propaldehyde thus obtained as its 2 : 4-dinitrophenylhydrazone. A higher-boiling fraction of the hydrolysis product is formulated as 3-hydroxy-2 : 2′ : 3′-trimercaptodipropyl sulphide (XI), which formed a crystalline di*iso*propylidene derivative (XII). When (IX) was treated with aqueous sodium carbonate under the same conditions as for the *cyclo*hexane compounds, the probable intermediate in the above reaction, 3-acetylthiopropylene sulphide (X), was obtained in 80% yield; it reacted slowly with methyl iodide to give trimethylsulphonium iodide, the formation of which, according to Culvenor, Davies, and Heath (*loc. cit.*), is a characteristic property of compounds containing the ethylene sulphide ring. Reaction of (X) with 2 : 3-dimercaptopropanol under alkaline conditions would clearly give (XI).

It was expected that (X) would be formed by similar treatment of 2 : 3-bisacetylthiopropanol (XIII), but some difficulty was experienced in the synthesis of the latter. The reaction of 2 : 3-dibromopropanol with potassium thiolacetate in boiling ethanol gave a

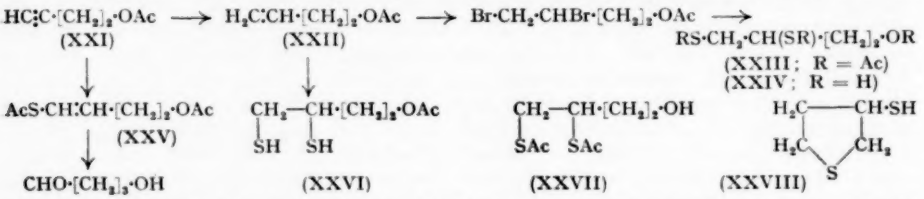
small quantity of what appeared to be a mixture of the required bisthiolacetate and its rearrangement product, but the main product was a polymer. Sjöberg (*Ber.*, 1942, **75**, 13) also attempted this reaction, but reported only its failure. When the dibromide was treated with thiolacetic acid in pyridine at 0°, only one bromine atom was replaced, and distillation of the product [probably (XIV)] effected substantial rearrangement to the thiol [probably (XV)]. The use of triethylamine brought about complete replacement of bromine, but intermolecular condensation apparently took place, since the product was almost entirely a polymer. However, acetylation of a solution of 2 : 3-dimercaptopropanol in two equivalents of aqueous sodium hydroxide, by shaking it with acetic anhydride, a method used for the acetylation of phenols (Chattaway, *J.*, 1931, 2495), gave a product which was mainly the required derivative. Treatment with sodium carbonate solution gave 3-acetylthiopropylene sulphide, identical with that obtained from the triacetyl compound.

Cyclisation of 2 : 3-dimercaptopropyl acetate (XVI) was effected under the same conditions, and gave 3-mercaptopropylene sulphide (XVII), together with a considerable quantity of polymer. Lazier and Signaigo (U.S.P. 2 396 597) had previously obtained (XVII) by thermal dehydration of 2 : 3-dimercaptopropanol, but had not proved its structure; this has now been effected by identification of the products of the acid-catalysed ring-fission. Heating of (XVII) with dilute hydrochloric acid gave a liquid with properties very similar to those of 2 : 3-dimercaptopropanol (XVIII), but it was shown to contain a small proportion of the isomeric 1 : 3-dimercaptopropan-2-ol (XIX) by desulphurisation with Raney nickel, oxidation of the product, and chromatographic separation of the 2 : 4-dinitrophenylhydrazones of the resulting carbonyl compounds; in this way some acetone 2 : 4-dinitrophenylhydrazone was detected in the presence of the main constituent, propaldehyde 2 : 4-dinitrophenylhydrazone. The formation of acetone provides conclusive proof of the structure (XVII), since (XX), the other possible dehydration or deacetylation product, could give only (XVIII) on hydrolysis. It is of interest that 2 : 3-dimercaptopropanol is the main product of the ring-fission, indicating a preferential opening of the sulphur–$C_{(1)}$ link, since Davies and Savige (*J.*, 1950, 317) have reported that when propylene sulphide is treated with hydrochloric acid it gives 2-chloropropanethiol, the bond between the sulphur and $C_{(2)}$ being broken. Nevertheless, the formation of some 1 : 3-dimercaptopropan-2-ol is of importance, because it indicates that a 1 : 3-dithiol can in certain circumstances arise from an acetylated 1 : 2-dithiol.

In order to determine to what extent the high reactivity of the 1-position in 2 : 3-dimercaptopropanol would be affected by the interposition of a methylene group, attention was next directed to the higher homologue, 3 : 4-dimercaptobutanol. Pavlic, Lazier, and Signaigo (*loc. cit.*) had obtained this dithiol by reaction of sodium hydrogen sulphide with 3 : 4-dibromobutanol, the latter being derived from but-3-en-1-ol, prepared, in poor yield, by the Grignard reaction of allyl iodide and formaldehyde. A better method appeared to be from but-3-yn-1-ol, readily available by reaction of sodium acetylide with ethylene oxide in liquid ammonia (Macallum, U.S.P. 2 125 384). Semi-hydrogenation of the butynyl acetate (XXI) in ethyl acetate solution over a palladium–charcoal catalyst gave but-3-en-1-yl acetate (XXII), which by addition of bromine and reaction of the dibromide with potassium thiolacetate in ethanol furnished triacetyl 3 : 4-dimercaptobutanol (XXIII); deacetylation with methanolic hydrogen chloride gave 3 : 4-dimercaptobutanol (XXIV). An alternative route, based on the addition of thiolacetic acid to (XXI), was also investigated, since this would be expected to give (XXIII) directly (cf. Bader, Cross, Heilbron, and Jones, *J.*, 1949, 619). The acetate was treated with excess of thiolacetic acid and a little ascaridole; heating for two hours at 100° gave mainly the mono-adduct, 4-acetylthiobut-3-en-1-yl acetate (XXV), the structure of which was confirmed by reaction with 2 : 4-dinitrophenylhydrazine in methanolic sulphuric acid, γ-hydroxybutaldehyde 2 : 4-dinitrophenylhydrazone being formed. Longer heating of the reactants, with either ascaridole or sulphuric acid catalyst, brought about some di-addition but no pure di-adduct could be separated. But-3-yn-1-ol itself reacted vigorously with thiolacetic acid, but no recognisable product could be isolated.

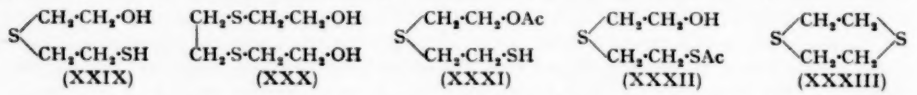
3 : 4-Dimercaptobutyl acetate (XXVI) and 3 : 4-bisacetylthiobutanol (XXVII) were

prepared from 3 : 4-dimercaptobutanol by methods similar to those used for the lower homologues. They were less reactive than their lower homologues, but with boiling aqueous sodium carbonate both gave some 3-mercaptothiophan (XXVIII), the properties



of which agreed with those recorded by Pavlic, Lazier, and Signaigo (*loc. cit.*) for a liquid obtained as a by-product in their preparation of 3 : 4-dimercaptobutanol; these authors suggested, but did not prove, the structure (XXVIII). This has now been done by selective hydrogenolysis, a solution of the compound in ethanol being heated for a short time with Raney nickel; the thiol group was preferentially reduced, and by interruption of the reaction at the appropriate time (indicated by estimation of thiol values) thiophan was obtained, and identified as its mercuric chloride complex. (The selective desulphurisation of mercaptothiazoles has been reported by Cook, Heilbron, and Levy, *J.*, 1947, 1598.)

In order to determine whether a six-membered ring could be formed by intramolecular deacetylation, a 1 : 5-hydroxy-thiol was required. That most readily accessible at the time was 2-hydroxy-2′-mercaptodiethyl sulphide (XXIX), which was prepared by the addition



of excess of ethanedithiol to ethylene oxide in ethanolic sodium ethoxide (cf. Owen and Smith, *loc. cit.*); a small proportion of 1 : 2-di-(2-hydroxyethylthio)ethane (XXX), previously described by Bennett and Whincop (*J.*, 1921, **119**, 1860), was also formed in this reaction. Monoacetylation of (XXIX) with acetic anhydride in acetic acid containing a little sulphuric acid gave the *O*-acetate (XXXI), whilst acetylation of the sodium derivative of (XXIX) in aqueous solution gave mainly the *S*-acetyl compound (XXXII). Neither (XXXI) nor (XXXII) gave any dithian (XXXIII) by alkaline deacetylation, although the free hydroxy-thiol was readily cyclised by treatment with hydrochloric acid.

The formation of cyclic sulphides by intramolecular deacetylation has not previously been observed, and the reaction provides a new illustration of the influence of sulphur, compared with oxygen, on the reactivity of neighbouring groups. Cyclic oxides can be prepared by alkaline hydrolysis of toluene-*p*-sulphonates, methanesulphonates, nitrates, and sulphates (cf. Peat, *Adv. Carbohydrate Chem.*, 1946, **2**, 37), but not of acetates; this is usually explained by the ease with which the first four types of esters undergo alkyl–oxygen fission, whereas with acetates acyl–oxygen fission is the rule. Although in the present work cyclisation has been found to occur both with *O*- and with *S*-acetyl derivatives, there is little doubt that the cyclic sulphide is actually formed only from the former, and that when an *S*-acetyl compound [*e.g.*, (II) or (IV)] is treated with alkali it is first converted into the *O*-acetyl isomer [(I) or (V)] (unpublished results by Mr. J. S. Harding). Ring-formation, therefore, must occur by removal of the acetoxy-group, *i.e.*, by the unusual alkyl–oxygen fission; this type of hydrolysis is known to be facilitated by electron-donating groups in the "alkyl" portion, and in the present instances the sulphur atom or atoms are clearly functioning in that way. It is noteworthy that the three- and five-membered sulphide rings are formed so easily, since the three- and five-membered oxide rings are those which are most readily formed by the alkaline hydrolysis of toluene-*p*-sulphonates, etc.

The greater stability towards hydrolysis shown by 3 : 4-dimercaptobutyl acetate compared with 2 : 3-dimercaptopropyl acetate is due to the interposition of the methylene group, which reduces the influence of the sulphur atoms on the linkage of the acetoxy-group to $C_{(1)}$, in general agreement with Bennett's conclusions on the effect of sulphur on the reactivity

of adjacent groups (*inter al.*, Bennett and Berry, *J.*, 1927, 1676). It would therefore be of interest to investigate the properties of the unknown 3 : 4-dimercaptobutyl chloride, in view of the high reactivity of the halogen in 2 : 3-dimercaptopropyl chloride and in 2 : 3-benzylidenedithiopropyl bromide (Miles and Owen, *J.*, 1950, 2938). Attempts to convert 3 : 4-dimercaptobutanol into the chloride by treatment with fuming hydrochloric acid, hydrogen chloride–zinc chloride in ether, or thionyl chloride, were unsuccessful, and a different method of approach was therefore investigated, involving the addition of thiolacetic acid to 4-chlorobut-1-yne. Reaction of but-3-yn-1-ol with thionyl chloride in cold pyridine gave di(but-3-ynyl) sulphite (XXXIV), but at 70°, in the presence of only a trace of pyridine (cf. Gerrard, *J.*, 1944, 85; Gerrard and French, *Nature*, 1947, **159**, 263), 4-chlorobut-1-yne was obtained in good yield; this reacted with thiolacetic acid, ascaridole being

$(HC{\equiv}C{\cdot}CH_2{\cdot}CH_2{\cdot}O)_2SO$ (XXXIV) $AcS{\cdot}CH{:}CH{\cdot}CH_2{\cdot}CH_2Cl$ (XXXV) $AcS{\cdot}CH_2{\cdot}CH(SAc){\cdot}CH_2{\cdot}CH_2Cl$ (XXXVI)

used as catalyst, to give a mixture of mono- and di-addition products. The lower-boiling fraction was shown to contain 1-acetylthio-4-chlorobut-1-ene (XXXV) by the formation of γ-chlorobutaldehyde on acid hydrolysis; the high-boiling material was mainly 3 : 4-bisacetylthiobutyl chloride (XXXVI). Hydrolysis of the latter with methanolic hydrogen chloride gave a product which probably contained 3 : 4-dimercaptobutyl chloride (since it gave 3-mercaptothiophan on treatment with alkali), but it could not be purified.

Although abnormal deacetylations have occurred more often under alkaline conditions, we have occasionally observed the formation of by-products when acetylated hydroxythiols have been boiled with N-methanolic hydrogen chloride, and in one instance (Evans, Fraser, and Owen, *loc. cit.*) a cyclic sulphide was isolated. It is well known that hydroxythiols undergo cyclisation and condensation to chain-polymers when they are treated with concentrated aqueous hydrochloric acid, the reactions occurring through sulphonium intermediates (Bell, Bennett, and Hock, *J.*, 1927, 1803; cf. Ray and Levine, *J. Org. Chem.*, 1937, **2**, 267; Bennett, *Trans. Faraday Soc.*, 1941, **37**, 794), and it is likely that this type of side reaction occurs to some extent even when the concentration of hydrogen chloride is quite small.

Experimental

(Except where otherwise stated, thiol values were determined by the method described in Part II, *J.*, 1949, 244; light petroleum refers to the fraction b. p. 40—60°.)

2-*Mercaptoethyl Acetate*.—To 2-mercaptoethanol (5 g.), containing a 10% solution of sulphuric acid in acetic acid (0·2 c.c.), acetic anhydride (6·8 g., 1 equiv.) was added during 10 minutes, the temperature being kept at *ca.* 40° by external cooling. The solution was then warmed in a water-bath at 60° for 1 hour, and finally left at room temperature for 20 hours. Ether (50 c.c.) was added, and the ethereal solution was washed three times with water and dried ($NaHCO_3$ and Na_2SO_4). Removal of the ether left a colourless liquid (8·2 g.), which on distillation gave a small low-boiling fraction and a main fraction of 2-mercaptoethyl acetate (5·5 g., 71%), b. p. 62—64°/16 mm., n_D^{20} 1·4612 (Found: thiol-S, 26·6. Calc. for $C_4H_8O_2S$: thiol-S, 26·7%). Nylen and Olsen (*loc. cit.*) give b. p. 52°/7 mm., n_D^{20} 1·4610.

The acetate (0·2 g.) was dissolved in 1 : 1 aqueous ethanol (20 c.c.), and 0·1N-sodium hydroxide (20 c.c.) was added. A white flocculent precipitate gradually formed, and there was a strong odour of ethylene sulphide. Under the same conditions, a solution of 2-mercaptoethanol remained clear and gave no ethylene sulphide.

trans-2-*Acetylthio*cyclo*hexanol*.—Thiolacetic acid (7·8 g., 0·1 mol.) was added to *cyclo*hexene oxide (10 g., 0·1 mol.); a bright yellow colour appeared, but rapidly faded. After 60 hours at room temperature the mixture had become more viscous, and was distilled. trans-2-*Acetylthio*cyclo*hexanol* (15 g., 84%), b. p. 72°/0·001 mm., n_D^{16} 1·5197, was thus obtained as a colourless liquid with a characteristic revolting odour (Found: S, 18·5. $C_8H_{14}O_2S$ requires S, 18·4%). Light absorption: max. 2340 Å, $\varepsilon = 4500$. Titration of a solution of the acetate in aqueous ethanol with iodine in the presence of only a trace of hydrochloric acid showed the presence of very little free thiol (Found: thiol-S, 0·5%). In N-hydrochloric acid, however, iodine continued to be taken up until a stable end-point was reached corresponding to the liberation of one free thiol group (Found: thiol-S, 18·5%); whether this was due to hydrolysis or to acyl migration was not established.

trans-2-*Mercapto*cyclo*hexyl Acetate*.—*trans*-2-Acetylthio*cyclo*hexanol (12 g.) with acetic

acid (0·1 g.) was kept at 100° for 13 hours; there was a change in odour and a decrease in viscosity. Distillation gave *trans*-2-mercapto*cyclo*hexyl acetate (11 g.) b. p. 106—108°/15 mm., n_D^{16} 1·4897 (Found: thiol-S, 18·5. Calc. for $C_8H_{14}O_2S$: thiol-S, 18·4%). Culvenor, Davies, and Heath (*loc. cit.*) give b. p. 109°/15 mm.

Alkaline Hydrolysis of trans-2-*Mercapto*cyclo*hexyl Acetate.*—(i) The acetate (2 g.) in a solution of sodium hydroxide (1·0 g.) in 50% aqueous ethanol (10 c.c.) was set aside for 12 hours. Dilution with water (50 c.c.), extraction with chloroform (50 c.c.), and concentration of the dried (Na_2SO_4) extract gave a viscous liquid (1·3 g.), which on distillation gave a trace of *cyclo*hexene sulphide, b. p. *ca.* 70°/15 mm., and 2-*hydroxy*-2′-*mercaptodi*cyclo*hexyl sulphide* (0·3 g.), b. p. 150—160°/0·2 mm. (Found: S, 26·0; thiol-S, 13·3. $C_{12}H_{22}OS_2$ requires S, 26·0; thiol-S, 13·0%). The residue was a colourless glass. The hydroxy-thiol (0·12 g.) in ethanol (1 c.c.), 1-chloro-2 : 4-dinitrobenzene (0·10 g.) in ethanol (0·5 c.c.), and sodium hydroxide (0·02 g.) in water (0·5 c.c.) were mixed, heated under reflux for 5 minutes, and filtered hot. Removal of the solvent and chromatography of the residual oil on alumina, with benzene as eluent, gave 2-*hydroxy*-2′-(2 : 4-*dinitrophenylthio*)*di*cyclo*hexyl sulphide* (0·1 g.) which crystallised from ethanol in yellow prisms, m. p. 128° (Found: N, 6·9. $C_{18}H_{24}O_5N_2S_2$ requires N, 6·8%).

Acidification of the alkaline solution remaining from the chloroform extraction, and further extraction with chloroform, gave a mobile liquid (0·6 g.) (Found: thiol-S, 16·0%). A portion (0·5 g.), on reaction with sodium hydroxide and 1-chloro-2 : 4-dinitrobenzene, as above, gave 2 : 4-dinitrophenyl *trans*-2-hydroxy*cyclo*hexyl sulphide (0·55 g.), m. p. 135° after chromatography and recrystallisation from ethanol. Culvenor and Davies (*loc. cit.*) give m. p. 134—135°.

(ii) *trans*-2-Mercapto*cyclo*hexyl acetate (3·5 g.) was added to a warm solution of sodium hydrogen carbonate (2·0 g.) in water (40 c.c.), which was then steam-distilled at 60°/150 mm. (under these conditions the reagent is effectively aqueous sodium carbonate). A colourless oil distilled over with the first drops of water, and continued to be formed for 30 minutes. The distillate was extracted with light petroleum, and the extract was dried (Na_2SO_4) and concentrated. Distillation of the residue (2·2 g.) gave *cyclo*hexene sulphide (1·6 g., 70%), b. p. 65—70°/15 mm., n_D^{15} 1·5245, and unchanged acetate (0·35 g., 10%), b. p. 75°/2 mm., n_D^{15} 1·4894. Culvenor, Davies, and Pausacker (*loc. cit.*) give b. p. 67—68°/16 mm., n_D^{20} 1·5309 for *cyclo*hexene sulphide.

trans-2-Mercapto*cyclo*hexanol gave no *cyclo*hexene sulphide when similarly treated.

Alkaline Hydrolysis of trans-2-*Acetylthio*cyclo*hexanol.*—The compound (0·5 g.) was treated with aqueous sodium hydrogen carbonate in the same way, and gave *cyclo*hexene sulphide (0·2 g.), b. p. 60—70°/15 mm., n_D^{15} 1·5232.

Alkaline Hydrolysis of the Triacetyl Derivative of 2 : 3-*Dimercaptopropanol.*—(i) The triacetyl derivative (16 g.) (Evans, Fraser, and Owen, *J.*, 1949, 248) was made up to 100 c.c. with 20% aqueous sodium hydroxide and shaken in a stoppered bottle. After 50 hours the maximum thiol value (57% of theory) was attained, and the solution was poured into 5N-hydrochloric acid (120 c.c.), with cooling. The resultant emulsion was extracted three times with ether, the extract was dried (Na_2SO_4), and the ether was removed by distillation. Fractionation of the residue (5 g.) gave: (1) 1·6 g., b. p. 71—75°/1 mm., n_D^{15} 1·5723 to 1·5733; (2) 1·1 g., b. p. 150—160°/0·001 mm., n_D^{15} 1·6190; (3) a viscous residue (2·3 g.). Constant ether-extraction of the aqueous solution for 12 hours gave a further 1·1 g., n_D^{15} 1·5722.

Fraction 1 was 2 : 3-dimercaptopropanol (Found: thiol-S, 51·2. Calc. for $C_3H_8OS_2$: thiol-S, 51·6%). A portion (0·2 g.) was dissolved in water (20 c.c.), Raney nickel (*ca.* 5 g.) was added, and the suspension was heated on the steam-bath for 4 hours. The nickel was removed by filtration, and the filtrate was boiled in a distillation flask during the addition of a 20% solution of potassium dichromate in 20% aqueous sulphuric acid. The distillate was collected in aqueous 2 : 4-dinitrophenylhydrazine sulphate, and gave propaldehyde 2 : 4-dinitrophenylhydrazone (0·1 g.), m. p. 155°, which was shown to be homogeneous by chromatography on alumina.

Fraction 2 was 3-*hydroxy*-2 : 2′ : 3′-*trimercaptodipropyl sulphide* (Found: S, 55·2; thiol-S, 40·4. $C_6H_{14}OS_4$ requires S, 55·6; thiol-S, 41·8%). A portion (0·4 g.) was dissolved in acetone (5 c.c.) and hydrogen chloride was passed in for 1 minute. Heat was evolved and after 10 minutes potassium carbonate was added to neutralise the acid and to dry the solution. Removal of acetone from the filtered solution left a semi-solid residue. Trituration with ethanol gave a white solid (0·1 g., m. p. *ca.* 110°), which gave the pure *diisopropylidene* derivative, m. p. 132°, after recrystallisation from methanol (Found: S, 41·5. $C_{12}H_{22}OS_4$ requires S, 41·3%).

(ii) The triacetyl derivative (1·0 g.) of 2 : 3-dimercaptopropanol was added to a warm solution of sodium hydrogen carbonate (1·1 g.) in water (20 c.c.), and the reaction mixture was

steam-distilled at 60°/150 mm. for 3 hours, a colourless oil passing over with the distillate. This was extracted with light petroleum, and the extracts on evaporation gave a mobile liquid with a sweet but obnoxious odour, which on distillation furnished *3-acetylthiopropylene sulphide* (0·5 g., 80%), b. p. 125°/40 mm., n_D^{18} 1·5525 (Found: S, 43·05; thiol-S, nil. $C_5H_8OS_2$ requires S, 43·25%). Light absorption: max. 2290 Å, $\varepsilon = 3500$. Treatment of this sulphide (0·2 g.) with methyl iodide (5 g.) for 2 weeks at room temperature gave a semi-solid product which on trituration with acetone furnished fine white needles (50 mg.), m. p. 205—210°. Recrystallisation from dry ethanol gave trimethylsulphonium iodide, m. p. 212°. Culvenor, Davies, and Heath (*loc. cit.*) give m. p. 215°.

2 : 3-*Bisacetylthiopropanol.*—(i) 2 : 3-Dibromopropanol (10 g.) was dissolved in dry pyridine (40 c.c.), and the solution was cooled to −5°. Thiolacetic acid (8·4 g.) was added dropwise, with stirring. After 64 hours at 0°, when some pyridine salt had crystallised out, the solution was poured into water (200 c.c.). Extraction with chloroform, and distillation of the extract (7·5 g.) showed that a mixture had been obtained, including an involatile polymer (3 g.). The higher-boiling fraction (0·8 g.) was re-distilled, and gave a mobile liquid, b. p. 60—62°/0·1 mm., n_D^{20} 1·5198, probably a mixture of 72% of *O*- and 28% of *S*-acetyl-2-bromo-3-mercaptopropanol (Found: S, 15·1; thiol-S, 10·9; Br, 37·8. Calc. for $C_5H_9O_2SBr$: S, 15·0; Br, 37·5%).

(ii) 2 : 3-Dimercaptopropanol (10 g.) was dissolved in a solution of sodium hydroxide (7·5 g.) in water (100 c.c.). The solution was cooled to 0°, and acetic anhydride (20 g.) was added in one portion; the mixture was vigorously stirred for 10 minutes and then allowed to separate into two layers. The upper aqueous portion was discarded, and the oil was washed twice with an equal volume of light petroleum, and then diluted with benzene, dried ($MgSO_4$), and evaporated under reduced pressure below 40° to give a viscous liquid (11·1 g.) consisting mainly of 2 : 3-bisacetylthiopropanol, containing a small proportion of free thiol (Found: Ac, 41·2; thiol-S, 3·1. Calc. for $C_7H_{12}O_3S_2$: Ac, 41·3%). Light absorption: max. 2300 Å, $\varepsilon = 7800$. Distillation of a portion at 100° (bath)/0·0001 mm. resulted in partial isomerisation, and gave a less viscous liquid (Found: thiol-S, 12·1%. Calc. for complete rearrangement: thiol-S, 15·4%).

Alkaline Hydrolysis of 2 : 3-*Bisacetylthiopropanol.*—The undistilled material (3 g.) was added to a warm solution of sodium hydrogen carbonate (4 g.) in water (40 c.c.) and steam-distilled at 60°/150 mm. for an hour. The distillate, which contained an upper oily layer, was extracted with light petroleum; distillation of the dried ($MgSO_4$) extract gave 3-acetylthiopropylene sulphide (1·2 g., 55%), b. p. 120°/35 mm., n_D^{23} 1·5500.

Alkaline Hydrolysis of 2 : 3-*Dimercaptopropyl Acetate.*—The acetate (7·2 g.) (Pavlic, Lazier, and Signaigo, *loc. cit.*) was added to a warm solution of sodium hydrogen carbonate (4 g.) in water (50 c.c.), and steam-distilled at 60°/150 mm., a light oil coming over with the first drops of distillate. After 1 hour, when no more oil was being collected, the distillate was extracted with light petroleum. The extract was dried (Na_2SO_4) and evaporated, and the residue was distilled, to give 3-mercaptopropylene sulphide (1·1 g., 27%), b. p. 66—67°/20 mm., n_D^{18} 1·5810 (Found: thiol-S, 31·2. Calc. for $C_3H_6S_2$: thiol-S, 30·2%). B.P. 597 368 gives b. p. 77°/30 mm., n_D^{25} 1·5799. Addition of phenyl *iso*cyanate (0·13 g.) to the thiol (0·1 g.) gave, after 2 hours, a *phenylurethane* (0·2 g.), m. p. 102° after recrystallisation from light petroleum (b. p. 60—80°) (Found: N, 6·5. $C_{10}H_{11}ONS_2$ requires N, 6·2%).

The steam-involatile material (3 g.) was a mixture of high-boiling polymers, from which no homogeneous product could be obtained.

Acid Ring-fission of 3-*Mercaptopropylene Sulphide.*—The mercapto-sulphide (1·0 g.), suspended in N-hydrochloric acid (30 c.c.) and acetic acid (10 c.c.), was heated on the steam-bath for 3 hours, most of the oil dissolving. Extraction with benzene gave a viscous liquid (0·9 g.), distillation of which gave a more mobile liquid (0·4 g.), b. p. 70—75°/1 mm., n_D^{19} 1·5710 (Found: thiol-S, 50·6. Calc. for $C_3H_8OS_2$: S, 51·6%). This mixture of 2 : 3-dimercaptopropanol and 1 : 3-dimercaptopropan-2-ol (0·3 g.) in water (20 c.c.) was heated on the steam-bath for 4 hours with Raney nickel (*ca.* 5 g.). The nickel was removed by filtration and the hot filtrate was oxidised by the addition of acid potassium dichromate solution. Distillation into aqueous 2 : 4-dinitrophenylhydrazine sulphate gave an orange precipitate (200 mg.) which was collected and chromatographed on alumina, with benzene as eluent; this separated acetone 2 : 4-dinitrophenylhydrazone (14 mg.), m. p. and mixed m. p. 126°, from the propaldehyde 2 : 4-dinitrophenylhydrazone (150 mg.), m. p. and mixed m. p. 156—157°.

But-3-yn-1-yl acetate, b. p. 77—78°/60 mm., n_D^{22} 1·4255 (Found: C, 64·4; H, 7·3. Calc. for $C_6H_8O_2$: C, 64·3; H, 7·2%), was prepared by acetylation of but-3-yn-1-ol with acetic anhydride and pyridine (cf. Jones, Shen, and Whiting, *J.*, 1950, 230).

Addition of Thiolacetic Acid to Butynyl Acetate.—Thiolacetic acid (13 g.) and ascaridole (0·05 c.c.) were added to butynyl acetate (5 g.). There was no evolution of heat, and the mixture was heated on the steam-bath for 2 hours. The unchanged materials (15 g.) were removed by distillation at 50 mm., and the red liquid residue was fractionated through a short column. The lower-boiling material (2·3 g.), b. p. 100—103°/5 mm., n_D^{25} 1·4985, was mainly 4-acetylthiobut-3-en-1-yl acetate (Found: S, 18·3. Calc. for $C_8H_{12}O_3S$: S, 17·1%). Light absorption: max. 2450, 2510 Å; $\varepsilon = 6600, 7100$. A portion (0·6 g.) was dissolved in a solution of 2 : 4-dinitrophenylhydrazine (1 g.) in methanol (20 c.c.) containing sulphuric acid (1 g.) and the solution was heated under reflux until no more hydrogen sulphide was evolved (8 hours). On cooling and addition of water, a crude solid (0·75 g.), m. p. 100—104°, was obtained. Recrystallisation from ethanol gave γ-hydroxybutaldehyde 2 : 4-dinitrophenylhydrazone, m. p. 113° (corr.) (Found: N, 20·9. Calc. for $C_{10}H_{12}O_5N_4$: N, 20·9%). Light absorption: max. 3560 Å, $\varepsilon = 21{,}400$. Adkins and Krsek (*J. Amer. Chem. Soc.*, 1948, **70**, 383) gave m. p. 178—179°, but this was a misprint for 108—109° (private communication).

Triacetyl Derivative of 3 : 4-*Dimercaptobutanol.*—A solution of but-3-yn-1-yl acetate (50 g.) in ethyl acetate (50 c.c.), with a 10% palladium–charcoal catalyst (1·2 g.), was shaken with hydrogen at atmospheric pressure until the required volume (10·95 l.) was taken up (4 hours). Removal of the catalyst by filtration, concentration, and distillation of the residue, gave but-3-en-1-yl acetate (49·7 g.), b. p. 58—59°/60 mm., n_D^{20} 1·4118 (Found: C, 63·0; H, 8·9. Calc. for $C_6H_{10}O_2$: C, 63·2; H, 8·8%). Pariselle (*Ann. Chim. Phys.*, 1911, [viii], **24**, 324) gives b. p. 125°, n_D^{15} 1·411.

Bromine (35 g.) in carbon tetrachloride (20 c.c.) was added dropwise to a solution of the butenyl acetate (25 g.) in carbon tetrachloride (50 c.c.) at 0°. 3 : 4-Dibromobutyl acetate (46 g., 55%) was thus obtained, having b. p. 84—85°/1 mm., n_D^{18} 1·5104. Pariselle (*loc. cit.*) records b. p. 135°/16 mm., n_D^{15} 1·508.

The dibromide (45 g.), potassium thiolacetate (41 g.), and thiolacetic acid (0·5 c.c.) in ethanol (200 c.c.) were heated under reflux for 6 hours. Most of the solvent was then removed under reduced pressure, and the residue was extracted with ether. The extracts were washed with water, dried (Na_2SO_4) and evaporated to give 3 : 4-*bisacetylthiobutyl acetate* (37 g., 80%), b. p. 110—112°/0·0001 mm., n_D^{22} 1·5150 (Found: C, 44·6; H, 6·05; S, 23·8. $C_{10}H_{16}O_4S_2$ requires C, 45·4; H, 6·1; S, 24·3%). Light absorption: max. 2300 Å, $\varepsilon = 8700$.

3 : 4-*Dimercaptobutanol.*—The triacetyl compound (45 g.) in 2% methanolic hydrogen chloride (200 c.c.) was heated under reflux for 4 hours, and the solvent was removed by distillation. The residue (30 g.) was shaken with water (600 c.c.), and the insoluble dark red oil (3·5 g.) was discarded. Extraction with light petroleum (100 c.c.) removed a further quantity (1·5 g.) of orange-red material. Further extraction with benzene (3 × 100 c.c.) gave almost pure 3 : 4-dimercaptobutanol as a pale yellow liquid (12 g.), b. p. 77—78°/0·0001 mm., n_D^{18} 1·5593 (Found: thiol-S, 45·8%). Finally, extraction with ether (3 × 200 c.c.) gave a colourless viscous oil (5 g.), distillation of which gave the pure dithiol, b. p. 70—71°/0·0001 mm., n_D^{23} 1·5572 (Found: thiol-S, 46·3. Calc. for $C_4H_{10}OS_2$: thiol-S, 46·4%). Pavlic, Lazier, and Signaigo (*loc. cit.*) give b. p. 96—97°/1 mm., n_D^{25} 1·5583.

The dithiol (0·7 g.) in ethanol (15 c.c.), sodium hydroxide (0·4 g.) in water (3 c.c.), and 1-chloro-2 : 4-dinitrobenzene (2·0 g.) in ethanol (10 c.c.) were mixed. Heat was evolved and the solution became orange, red, then brown, and an oil was deposited on the walls of the flask. The mixture was heated under reflux for 5 minutes, and then filtered hot. On cooling and dilution with water, a crude solid (0·35 g.) was obtained. Recrystallisation from 5 : 1 methanol–nitrobenzene gave 3 : 4-*di*-(2 : 4-*dinitrophenylthio*)*butanol*, bright yellow needles, m. p. 183° (Found: C, 41·0; H, 2·9; N, 11·7. $C_{16}H_{14}O_9N_4S_2$ requires C, 40·9; H, 3·0; N, 11·9%).

3 : 4-*Dimercaptobutyl Acetate.*—Acetic anhydride (7·8 g.) was added in small portions to the dithiol (10 g.) containing 0·2 c.c. of a 10% solution of sulphuric acid in acetic acid, the temperature being kept between 30° and 40°. The solution was then warmed at 60° for 1 hour and left at 20° for 20 hours. Ether was added, and the solution was washed with water, dried ($NaHCO_3$ and $MgSO_4$), and evaporated to an oil (13·5 g.). Fractionation gave 3 : 4-*dimercaptobutyl acetate* (4 g.). b. p. 65—66°/0·0001 mm., n_D^{20} 1·5208 (Found: S, 35·5; thiol-S, 35·2. $C_6H_{12}O_2S_2$ requires S, 35·6%). Light absorption: no high-intensity max. above 2200 Å.

3 : 4-*Bisacetylthiobutanol* (with J. S. Harding).—Acetic anhydride (5 g.) was added, with shaking and cooling, to a solution of 3 : 4-dimercaptobutanol (3 g.) and sodium hydroxide (1·75 g.) in water (25 c.c.) at 0°. After 10 minutes the lower layer was removed and washed twice with light petroleum, the washings being rejected; the oil was then diluted with benzene, dried ($MgSO_4$), and evaporated below 40° under reduced pressure. The product contained some

triacetyl derivative (Found : 2·4 acetyl groups per mol.) and was therefore dissolved in 5 volumes of methanol and extracted several times with light petroleum. Evaporation of the methanolic solution below 40° gave an oil which was essentially the required di-*S*-acetyl derivative, containing only a small proportion of free thiol and triacetyl derivative (Found : S, 27·2; thiol-S, 2·2; Ac, 40·2. Calc. for $C_8H_{14}O_3S_2$: S, 28·8; Ac, 38·7%). Light absorption : max. 2300 Å, $\varepsilon = 7550$.

Alkaline Hydrolysis of the Acetyl Derivatives of 3 : 4-*Dimercaptobutanol* (with J. S. Harding). —(i) 3 : 4-Dimercaptobutyl acetate (2 g.) was boiled under reflux for 20 minutes with a solution of sodium hydrogen carbonate (2·7 g.) in water (80 c.c.); the mixture was then distilled in steam until no more oil was collected. Extraction of the distillate with light petroleum, and evaporation of the dried ($MgSO_4$) extracts, gave 0·3 g., which on distillation furnished 3-*mercaptothiophan* (0·2 g.), b. p. 95°/30 mm., n_D^{20} 1·5780 (Found : C, 40·0; H, 6·7; S, 52·4; thiol-S, 26·3. $C_4H_8S_2$ requires C, 40·0; H, 6·7; S, 53·4; thiol-S, 26·7%). Treatment with phenyl *iso*cyanate for an hour at ordinary temperature gave the *phenylurethane*, which crystallised from light petroleum (b. p. 60—80°) in needles, m. p. 106° (Found : C, 55·8; H, 5·6; N, 5·9. $C_{11}H_{13}ONS_2$ requires C, 55·2; H, 5·5; N, 5·9%).

(ii) Similar treatment of 3 : 4-bisacetylthiobutanol (1·2 g.) gave 3-mercaptothiophan (0·1 g.), b. p. 85—90°/20 mm., n_D^{19} 1·5790.

(iii) Triacetyl 3 : 4-dimercaptobutanol (5 g.) was boiled under reflux for 4 hours with sodium hydrogen carbonate (15 g.) in water (40 c.c.). Steam-distillation, and isolation as before, gave 3-mercaptothiophan (0·25 g.), b. p. 93°/25 mm., n_D^{22} 1·5760.

Partial Desulphurisation of 3-*Mercaptothiophan.*—The compound (0·35 g.) was dissolved in ethanol (30 c.c.) and Raney nickel (1 g.) was added. After 15 minutes' heating under reflux, a sample (0·5 c.c.) was withdrawn, filtered, acidified with hydrochloric acid, and titrated with iodine; the thiol value indicated 75% removal of the SH group. After a further 5 minutes (when the titration indicated 80% reaction) the solution was cooled and filtered. The filtrate was diluted with an equal volume of water, and a solution of mercuric chloride (1 g.) in water (20 c.c.) was added. The precipitate was collected and dried (0·45 g.; m. p. 120—125°). Recrystallisation from aqueous alcohol gave white needles of the mercuric chloride complex of thiophan, m. p. and mixed m. p. 123—125°.

2-*Hydroxy*-2′-*mercaptodiethyl Sulphide.*—Ethylene oxide (3·5 g.) was dissolved in ethanol (100 c.c.) at 0° contained in a wide-mouthed bottle, and sodium (0·2 g.) was added. A test-tube containing ethane-1 : 2-dithiol (9 g.) was supported in the bottle, which was then securely stoppered, cooled in ice, and inverted, and the contents were mixed. After a short time the solution became warm. After 14 hours at room temperature, the bottle was opened, and solid carbon dioxide was added to neutralise the sodium. The solution was concentrated, ether was added to the residue, and the sodium salts were removed by filtration. Evaporation of the ether, and fractionation of the residual oil (8 g.), separated the 2-*hydroxy*-2′-*mercaptodiethyl sulphide* (4·2 g., 38%), b. p. 106°/0·5 mm., n_D^{19} 1·5622 (Found : S, 46·2; thiol-S, 23·3. $C_4H_{10}OS_2$ requires S, 46·4; thiol-S, 23·2%), from the 1 : 2-di-(2-hydroxyethylthio)ethane (1·0 g., 14%), b. p. 170°/0·5 mm., white plates, m. p. 64° after one recrystallisation from ether. Bennett and Whincop (*J.*, 1921, **119**, 1860) also give m. p. 64°.

Alkaline Hydrolysis of the O- *and the* S-*Acetyl Derivative of* 2-*Hydroxy*-2′-*mercaptodiethyl Sulphide.*—The hydroxy-thiol (3·5 g.) was acetylated with acetic anhydride (2·7 g.) and a 10% solution of sulphuric acid in acetic acid (0·2 c.c.) in the same way as for 2-mercaptoethanol, but the reaction did not proceed with the same degree of selectivity. Careful fractionation, however, gave the O-*acetate* (0·8 g.), b. p. 98—100°/0·5 mm., n_D^{1} 1·5269 (Found : S, 36·6; thiol-S, 18·0. $C_6H_{12}O_2S_2$ requires S, 35·6; thiol-S, 17·8%). This product (0·6 g.) was dissolved in a solution of sodium hydroxide (0·5 g.) in water (10 c.c.), and steam-distilled for an hour. The solution remained homogeneous, and the distillate was clear and odourless.

(With J. S. Harding). Acetic anhydride (1·05 g.) was added to a solution of the hydroxy-thiol (1·4 g.) and sodium hydroxide (0·4 g.) in water (15 c.c.) at 0°. After 10 minutes, extraction with benzene and evaporation of the dried (Na_2SO_4) extracts gave an oil, which on distillation furnished the S-*acetyl* derivative (0·93 g.), b. p. 108—110°/0·4 mm., n_D^{20} 1·5338 (Found : C, 39·9; H, 6·8; thiol S, 0·9. $C_6H_{12}O_2S_2$ requires C, 40·0; H, 6·7%). Light absorption : max. 2270, 2360 Å; $\varepsilon = 4670$, 3400. Treatment with alkali, as for the *O*-acetate, again gave no dithian.

Dithian from 2-*Hydroxy*-2′-*mercaptodiethyl Sulphide.*—The hydroxy-thiol (0·5 g.) was added to hydrochloric acid (15 c.c.; *d* 1·16). It dissolved immediately, but the solution rapidly became cloudy, and a flocculent precipitate was formed. After 12 hours this was collected, washed with

water, and dried (0·2 g.; m. p. 65—80°). It contained halogen, and was involatile at 60°/15 mm. though after such heating it showed m. p. 75—80°. The original aqueous acid filtrate on steam-distillation gave dithian (0·03 g.) and involatile polymer (0·25 g.); the latter, on crystallisation from ethanol, gave a main fraction, m. p. 78—80°, apparently identical with that described above (Found: S, 46·9; Cl, 9·1%). Depolymerisation was effected by heating 0·2 g. in phenol (1 g.) at 160—180° for 3 hours in a sealed tube; hydrogen chloride was liberated. The product was washed with sodium hydroxide, and the insoluble residue (0·15 g.) on steam-distillation gave dithian (0·07 g.), m. p. 110°.

4-Chlorobut-1-yne.—(i) But-3-yn-1-ol (4·6 g.) was dissolved in pyridine (50 c.c.), and the solution was cooled to 0°. Thionyl chloride (8 g.) was added slowly with constant shaking, the temperature being kept below 5°. Pyridine hydrochloride separated out almost immediately. After 1 hour at 0°, ice was added, followed by cold 2N-sulphuric acid. Extraction with ether, and distillation of the extracted material, gave a small quantity of low-boiling liquid, followed by *dibut-3-ynyl sulphite* (5·2 g., 85%), b. p. 124—126°/15 mm., n_D^{15} 1·4750 (Found: S, 17·2. $C_8H_{10}O_3S$ requires S, 17·2%). The liquid was soluble in warm 2N-sodium hydroxide, and on acidification of the solution sulphur dioxide was evolved.

(ii) Thionyl chloride (9 g.) was added to but-3-yn-1-ol (5·4 g.), containing a trace of pyridine (*ca.* 0·1 c.c.), cooled in ice. The mixture was then heated under reflux on a water-bath at 70° for 3 hours. Direct distillation gave a small quantity of thionyl chloride, and then *4-chlorobut-1-yne* (5·2 g., 76%), b. p. 78°, n_D^{16} 1·4420 (Found: C, 54·3; H, 5·9. C_4H_5Cl requires C, 54·3; H, 5·7%).

Addition of Thiolacetic Acid to 4-Chlorobut-1-yne.—(i) Thiolacetic acid (6 g.) was added to 4-chlorobut-1-yne (1·8 g.) containing ascaridole (0·1 c.c.). When the mixture was warmed to 30°, a vigorous exothermic reaction began; when this had subsided, the product was heated under reflux on the steam-bath for 1 hour, and excess of thiolacetic acid (2·8 g.) was removed by distillation at 100 mm. The residue was distilled and gave a lower-boiling fraction (2·5 g.), b. p. 79—80°/2 mm., n_D^{15} 1·5287, which was a mixture of the mono- and di-adduct (Found: S, 24·7; Cl, 16·6. Calc. for a mixture of C_6H_9OClS 27% and $C_8H_{13}O_2ClS_2$ 73%: S, 24·7; Cl, 16·5%). Light absorption: max. 2510 Å, $E^{1\%}_{1\,cm.}$ 425.

This product (1 g.) was added to a solution of 2 : 4-dinitrophenylhydrazine (2 g.) in methanol (30 c.c.), containing sulphuric acid (1·3 g.), and boiled under reflux until no more hydrogen sulphide was evolved (5 hours). γ-Chlorobutaldehyde 2 : 4-dinitrophenylhydrazone separated from the cooled solution; after recrystallisation from methanol it formed pale orange plates, m. p. 134°. Paul (*Compt. rend.*, 1942, **215**, 303) gives m. p. 134—135°.

(ii) Thiolacetic acid (14 g.) was added to 4-chlorobut-1-yne (4·2 g.) containing ascaridole (0·2 c.c.), and the mixture was heated on the steam-bath for 3 hours. The excess of thiolacetic acid (6·8 g.) was removed, and the residue was distilled. The lower-boiling material (4·9 g.), b. p. 75—85°/1·5 mm., n_D^{15} 1·5253—1·5294, contained some mono-adduct (see above); the higher-boiling fractions (4 g.), b. p. 108—111°/0·2 mm., were redistilled and gave substantially pure 3 : 4-*bisacetylthiobutyl chloride*, b. p. 92°/0·0001 mm., n_D^{15} 1·5392 (Found: S, 27·4; Cl, 14·1. $C_8H_{13}O_2ClS_2$ requires S, 26·6; Cl, 14·7%). Light absorption: Max. 2280, 2320 Å; ε = 9100. The high sulphur and low chlorine analysis was probably caused by the presence of a small proportion of 1 : 3 : 4-trisacetylthiobutane, formed by slow reaction of the halogen with thiolacetic acid; benzyl chloride, heated for 72 hours at 100° with an equal weight of thiolacetic acid, gave 5% of benzyl thiolacetate, b. p. 105°/12 mm., n_D^{16} 1·5612.

3-Mercaptothiophan from 3 : 4-Bisacetylthiobutyl Chloride.—The bisthiolacetate (6 g.) was heated under reflux in 2% methanolic hydrogen chloride (60 c.c.) for 2·5 hours. The solvent was removed on the steam-bath, and the product was distilled, to give a pale orange oil (1·1 g.), b. p. 60—75°/0·2 mm., n_D^{16} 1·5708; this product (1·0 g.) was added to a warm solution of sodium hydrogen carbonate (0·6 g.) in water (20 c.c.), and steam-distilled at 60°/150 mm., a light oil being collected in the distillate. This was extracted with light petroleum, and on distillation gave 3-mercaptothiophan (0·3 g.), b. p. 78°/15 mm., n_D^{16} 1·5750 (Found: thiol-S, 26·1. Calc. for $C_4H_8S_2$: thiol-S, 26·7%), characterised as the phenylurethane, m. p. and mixed m. p. 106°.

We are glad to acknowledge the financial support afforded by the Medical Research Council in the purchase of certain special chemicals and in the provision of a grant (to L. W. C. M.). Absorption spectra were determined by Mrs. A. I. Boston, and the analyses were carried out in the Organic Microanalytical Laboratory by Mr. F. H. Oliver and his staff.

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150. *The Synthesis of Thyroxine and Related Substances. Part IX.* Analogues of Thyroxine with Modified Side Chains.*

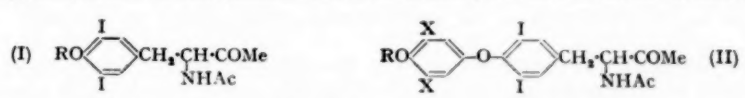
By R. C. Cookson and G. F. H. Green.

3 : 5-Di-iodothyronine and thyroxine have been converted into analogues of thyroxine with the alanine side chain replaced by other groups, in the hope of producing antagonists of the hormone.

3 : 5-Di-iodotyrosine, 3 : 5-di-iodothyronine, and thyroxine were converted by acetic anhydride in pyridine into the expected methyl α-acetamido-ketones, which were cyclised with phosphoryl chloride to the 2 : 5-dimethyl-oxazoles.

Exhaustive methylation and Hofmann degradation of 3 : 5-di-iodothyronine and thyroxine led to the corresponding methylated unsaturated acids (V; R = Me, X = H) and (V; R = Me, X = I) respectively. Demethylation and iodination of the former product yielded the acrylic acid analogue (V; R = H, X = I) of thyroxine. These cinnamic acids reacted with hydroxylamine to give either the oxime of the corresponding acetophenone or the β-amino-acid, or a mixture of both. β-Thyroxine † was made by iodination of 3 : 4-di-iodo-β-thyronine prepared in this way.

A modification of the molecule of essential amino-acids that has often led to the production of metabolic antagonists is the substitution of a methyl group (radius 2·0 Å) for the hydroxyl (radius 1·7 Å) of the carboxyl group. Ketones of this kind have been shown to inhibit the effects of *p*-aminobenzoic acid (Auhagen, *Z. physiol. Chem.*, 1942, **274**, 48; Kuhn, Moller, Wendt, and Beinert, *Ber.*, 1942, **75**, 711), nicotinic acid (Woolley, *J. Biol. Chem.*, 1945, **157**, 455; Gaebler and Beher, *ibid.*, 1951, **188**, 343), and pantothenic acid (Woolley and Collyer, *J. Biol Chem.*, 1945, **159**, 263) to varying degrees in bacteria or mammals; and the methyl α-amino-ketones corresponding to leucine, valine, *iso*leucine, and tyrosine prevent regrowth of the tails of tadpoles after amputation, although admittedly there is no proof that this is due to their direct interference with the metabolism of these amino-acids (Lehmann, Bretscher, Kühne, Sorkin, Erne, and Erlenmeyer, *Helv. Chim. Acta*, 1950, **33**, 1217). The hydrolysis of *N*-benzoyl- and *N*-acetyl-L-tyrosinamide catalysed by chymotrypsin is specifically inhibited by 3-acetamido-4-phenyl- and 3-acetamido-4-*p*-hydroxyphenylbutan-2-one (Kaufman and Neurath, *J. Biol. Chem.*, 1949, **181**, 623).



Although the few tested modifications of the thyroxine side chain have produced compounds with varying degrees of thyroxine activity (Frieden and Winzler, *J. Biol. Chem.*, 1948, **176**, 155), we attempted the preparation of the methyl ketone corresponding to thyroxine as a possible antagonist.

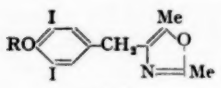
The amino-acids, 3 : 5-di-iodo-L-tyrosine, 3 : 5-di-iodo-L-thyronine, and L-thyroxine, reacted in boiling pyridine with a large excess of acetic anhydride (Levene and Steiger, *J. Biol. Chem.*, 1927, **74**, 689; 1928, **79**, 95; Dakin and West, *ibid.*, 1928, **78**, 91, 745; Cleland and Niemann, *J. Amer. Chem. Soc.*, 1948, **71**, 841), evolving carbon dioxide and producing the DL-acetamido-acetoxy-ketones (I; R = Ac), (II; R = Ac; X = H), and (II; R = Ac; X = I) respectively. The compound (I; R = Ac) could not be induced to crystallise, but treatment with hot sodium carbonate solution yielded the crystalline hydroxy-compound (I; R = H).

* Part VIII, *J.*, 1951, 2467.

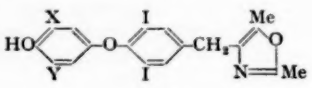
† The β-amino-acids, β-amino-β-(4-*p*-hydroxyphenoxyphenyl)propionic acid and β-amino-β-[4-(4′-hydroxy-3′ : 5′-di-iodophenoxy)-3 : 5-di-iodophenyl]propionic acid (VII; R = H, X = I), isomeric with the α-amino-acids, thyronine and thyroxine, are referred to here as " β-thyronine " and " β-thyroxine " respectively.

Cyclisation of the methyl α-acetamido-ketone grouping in these compounds gave access to a series of analogues containing the 2 : 5-dimethyloxazole group. When the ketone (II; R = Ac; X = H) from di-iodothyronine was treated with sulphuric acid, the usual dehydrating agent for such cyclisations (Wiley, *Chem. Reviews*, 1945, **37**, 40), the resulting oxazole contained a sulphonic acid group, presumably next to the hydroxyl group, *i.e.*, to give (IV; X = SO_3H; Y = H).

Cyclisation of the three acetamido-ketones proceeded smoothly, however, in phosphoryl chloride on the steam-bath. Hydrolysis of a solution of (I; R = H) in phosphoryl chloride gave a clear aqueous solution from which the organic matter could be extracted with chloroform only after boiling, suggesting that the oxazole (III; R = H) had originally been present as a phosphoric ester. In the same way, heating the reaction mixture of (II; R = Ac; X = H) and phosphoryl chloride with water (to hydrolyse the *O*-acetyl group) gave (IV; X = Y = H). Similar treatment of the tetra-iodo-compound (II; R = Ac; X = I) yielded a substance thought to be solvated (IV; X = Y = I) until the authentic hydroxy-compound was made by iodination of (IV; X = Y = H) and found



(III)



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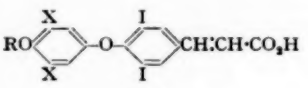


(V)

different. The product of direct cyclisation was then shown to be the acetyl derivative of (IV; X = Y = I): it contained an acetyl group and gave a negative Kendall test with nitrous acid and ammonia. The survival of the acetyl group in the tetra-iodo-, but not in the di-iodo-, compound is probably due to the lower solubility of the former in aqueous acid.

As *N*-acetyl-*O*-benzyl-3 : 5-di-iodotyrosine antagonises thyroxine in tadpoles (Woolley, *J. Biol. Chem.*, 1946, **164**, 11; Frieden and Winzler, *ibid.*, 1949, **179**, 423), the acetamido-ketone (I; R = H) from di-iodotyrosine was condensed with benzyl chloride in ethyl methyl ketone containing potassium carbonate, to give the benzyl ether (I; R = C_6H_5·CH_2) The corresponding oxazole (III; R = H), however, was recovered unchanged after the same treatment, although it condensed normally when the sodium salt was boiled with benzyl chloride in ethanol.

Acid hydrolysis of (II; R = Ac or H; X = I) under various conditions gave gums from which no crystalline salt of the amino-ketone corresponding to thyroxine could be isolated.

The acrylic acid analogue of thyroxine (V; R = H, X = I), the methyl ether of which was prepared by Hofmann degradation of thyroxine during the classical work on the hormone (Harington and Barger, *Biochem. J.*, 1927, **21**, 169), as well as being a versatile starting material for further transformations, is itself of some interest as a possible antagonist, by analogy with the competition of indolylacrylic acid with tryptophan in bacteria (Fildes, *ibid.*, 1938, **32**, 1600). Exhaustive methylation and alkaline treatment of thyroxine, following Corti's method for the Hofmann degradation of tyrosine (*Helv. Chim. Acta*, 1949, **32**, 681), gave (V; R = Me, X = I) in high yield. This substance could not be demethylated by hydriodic acid in acetic acid owing to its extremely low solubility. With phenol as solvent, demethylation occurred, but the product appeared to be chiefly (V; R = X = H), showing that reduction or trans-iodination with the solvent had also taken place. The di-iodo-compound (V; R = Me, X = H), got by Hofmann degradation of 3 : 5-di-iodothyronine, also in excellent yield, was demethylated, however, without difficulty. The product was then iodinated to the acrylic acid analogue of thyroxine (V; R = H, X = I). After this work was complete the synthesis of (V; R = H, X = H and I) from 3 : 5-di-iodo-4-*p*-methoxyphenoxybenzaldehyde was reported by Wawzonek, Wang, and Lyons (*J. Org. Chem.*, 1950, **15**, 593); the melting or decomposition points of both compounds were given as about 40° below those reported here.

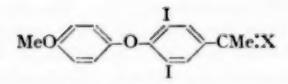
A little known reaction of cinnamic acid is its conversion by hydroxylamine into a

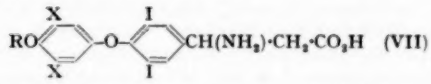
mixture of β-amino-β-phenylpropionic acid and acetophenone oxime (Posner, *Ber.*, 1905, **38**, 2320; *Annalen*, 1912, **389**, 120; Steiger, *Org. Synth.*, 1942, **22**, 26):

$$Ph\cdot CH{:}CH\cdot CO_2H \longrightarrow Ph\cdot CH(NH\cdot OH)\cdot CH_2\cdot CO_2H \longrightarrow Ph\cdot CH(NH_2)\cdot CH_2\cdot CO_2H$$

$$\downarrow$$

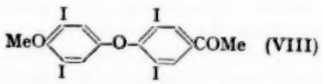
$$HO\cdot N{:}CPh\cdot CH_2\cdot CO_2H \longrightarrow HO\cdot N{:}CPhMe$$

(VI) 

 (VII)

When boiled with a solution of hydroxylamine in alcohol–dioxan the di-iodocinnamic acid (V; R = Me, X = H) gave a mixture of the ketoxime (VI; X = N·OH) (36% yield) and 3 : 5-di-iodo-β-thyronine methyl ether (VII; R = Me, X = H) (25% yield). The constitution of both products was definitely established. The oxime reacted with 2 : 4-dinitrophenylhydrazine hydrochloride with formation of the 2 : 4-dinitrophenylhydrazone, and on hydrolysis gave the ketone (VI; X = O), degraded by iodine in alkaline solution to iodoform and 3 : 5-di-iodo-4-*p*-methoxyphenoxybenzoic acid, identical with an authentic sample (Part I, *J.*, 1949, S 185). The second product (VII; R = Me, X = H) behaved as a typical β-amino-acid. It yielded an acetyl derivative, and lost ammonia above its melting point, regenerating the methoxy-cinnamic acid (V; R = Me, X = H). Treatment with hydriodic acid in acetic acid resulted in loss of ammonia as well as demethylation, to give the hydroxy-cinnamic acid (V; R = X = H).

Reaction of the tetra-iodocinnamic acid (V; R = Me, X = I) with hydroxylamine under similar conditions led, on the other hand, to the oxime of the methyl ketone (VIII) as the only isolated product (41%); even a small proportion of β-amino-acid could hardly have been overlooked because of the very low solubility of such a compound. The oxime could not be obtained crystalline, nor initially could the ketone (VIII) itself. The product was therefore converted into the 2 : 4-dinitrophenylhydrazone, which was purified by chromatography and then hydrolysed back to the free ketone with acetone containing hydrochloric acid. A second experiment, in which the product was hydrolysed directly to the ketone, gave a lower yield.

 (VIII)

One of the objectives of this work was the production of β-thyroxine (VII; R = H, X = I) and its derivatives. After the failure of the last reaction to lead to any of the methyl ether, the shortest route to β-thyroxine seemed to be to iodinate 3 : 5-di-iodo-β-thyronine. The latter could not be got from its methyl ether, but resulted, though in rather poor yield, from the reaction of the hydroxycinnamic acid (V; R = X = H) with hydroxylamine. It was smoothly iodinated with potassium tri-iodide in aqueous ethylamine (Part VI; *J.*, 1950, 840) to β-thyroxine.

The antithyroid potencies of the above compounds were examined by Maclagan and Sheehan's method (*J. Endocrinol.*, 1950, **6**, 456), but none showed significant activity.

Experimental

DL-3-*Acetamido*-4-(4-*hydroxy*-3 : 5-*di-iodophenyl*)*butan*-2-*one* (I; R = H).—3 : 5-Di-iodo-L-tyrosine (25 g.) was dissolved in a mixture of dry pyridine (150 ml.) and acetic anhydride (60 ml.), and the solution was heated under reflux for 2½ hours. No further carbon dioxide evolution could be detected after 2 hours. Chloroform (100 ml.) was added to the cooled pyridine solution, and the whole stirred below 20° with excess of 2N-hydrochloric acid to remove the pyridine. A similar treatment of the chloroform solution with 2N-sodium carbonate hydrolysed excess of acetic anhydride, the stirring being continued for 1 hour. The chloroform was dried azeotropically by concentration to about 50 ml. and passed down an alumina column. Most of the tarry impurities were adsorbed and the product passed straight through as a yellow solution.

This was taken to dryness *in vacuo*, the gum was dissolved in a little ethanol, and anhydrous sodium carbonate (40 g.) was added as a strong aqueous solution. After steam had been blown in for 1 hour, the cooled aqueous solution was decanted from the small tarry residue, acidified, and extracted with chloroform (3 × 50 ml.) which was concentrated to dryness. The resulting gum crystallised from ethyl acetate, to give nearly white needles of the *ketone*, m. p. 150—152° (12·0 g., 44%) (Found: C, 30·4; H, 2·8; I, 54·1. $C_{12}H_{13}O_3NI_2$ requires C, 30·5; H, 2·7; I, 53·7%).

DL-3-*Acetamido*-4-(4-p-*acetoxyphenoxy*-3 : 5-*di-iodophenyl*)*butan*-2-*one* (II; R = Ac, X = H).—3 : 5-Di-iodo-L-thyronine was treated as above. After removal of the pyridine and excess of acetic anhydride the product was chromatographed in benzene on alumina. Elution with a mixture of benzene and acetone (equal parts by volume) removed a yellow band. On evaporation of the eluate a gum remained which was crystallised twice from ethyl acetate and *cyclo*hexane, yielding the *ketone* as white crystals, m. p. 126—130° (4·8 g. from 10 g., 42%) (Found: C, 39·7; H, 3·5; I, 41·0. $C_{20}H_{19}O_5NI_2$ requires C, 39·6; H, 3·2; I, 41·8%).

The ketone (0·25 g.) was dissolved in ethanol (3 ml.) with gentle heat and added to a solution of 2 : 4-dinitrophenylhydrazine (0·09 g.) in sulphuric acid (1 ml.) and ethanol (3 ml.). The mixture was warmed on the steam-bath for 30 minutes. Addition of water precipitated the 2 : 4-*dinitrophenylhydrazone* which was crystallised twice from ethanol to yield bright yellow crystals, m. p. 130° (Found: N, 8·7; I, 32·4. $C_{24}H_{21}O_6N_5I_2$ requires N, 8·8; I, 32·1%).

DL-3-*Acetamido*-4-[4′-(4″-*acetoxy*-3″ : 5″-*di-iodophenoxy*)-3′ : 5′-*di-iodophenyl*]*butan*-2-*one* (II; R = Ac, X = I).—L-Thyroxine was treated as before and the pyridine and acetic anhydride were removed. The chloroform solution was evaporated to dryness and the gum crystallised from ethyl acetate, to yield white crystals of the *ketone*, m. p. 223—226° (10·5 g. from 25 g.; 38%) (Found: C, 28·1; H, 2·1; I, 58·8. $C_{20}H_{17}O_5NI_4$ requires C, 28·0; H, 2·0; I, 59·1%).

DL-3-*Acetamido*-4-[4′-(4″-*hydroxy*-3″ : 5″-*di-iodophenoxy*)-3′ : 5′-*di-iodophenyl*]*butan*-2-*one* (II; R = H, X = I).—The mother-liquor from the previous preparation was concentrated to dryness *in vacuo* and chromatographed in benzene on alumina. The yellow solution which passed through contained nothing of consequence, but with a mixture of benzene and acetone (equal parts by volume) a brown fraction was eluted. On removal of the solvent the residue crystallised. Recrystallisation from aqueous dioxan yielded the *ketone* as white needles, m. p. 253—254° with frothing (3·5 g., total yield including acetoxy-compound, 51%) (Found: C, 29·3; H, 2·3; I, 56·1. $C_{18}H_{15}O_4NI_4$ requires C, 29·2; H, 2·6; I, 56·1%).

4-(4-*Hydroxy*-3 : 5-*di-iodobenzyl*)-2 : 5-*dimethyloxazole* (III; R = H).—DL-3-Acetamido-4-(4-hydroxy-3 : 5-di-iodophenyl)butan-2-one (10 g.) was warmed in phosphorus oxychloride (15 ml.) on the steam-bath for 1 hour. Dissolution occurred rapidly and the mixture darkened somewhat. After cooling, the solution was poured carefully into water (150 ml.) to hydrolyse the phosphorus oxychloride. No special precautions were taken to prevent heating, and almost all the product remained in solution. The strongly acid liquid was then boiled under reflux for 1 hour, cooled, and extracted with chloroform (3 × 50 ml.). Some tarry matter remained undissolved. The chloroform was removed *in vacuo* and the residual gum crystallised from ethyl acetate. The *oxazole* formed white needles, m. p. 200—201° (decomp.) (6·8 g., 71%) (Found: C, 31·7; H, 2·3; I, 55·4. $C_{12}H_{11}O_2NI_2$ requires C, 31·7; H, 2·4; I, 55·8%).

4-(4-p-*Hydroxyphenoxy*-3 : 5-*di-iodobenzyl*)-2 : 5-*dimethyloxazole* (IV; X = Y = H).—DL-3-Acetamido-4-(4-*p*-acetoxyphenoxy-3 : 5-di-iodophenyl)butan-2-one (5 g.) was heated in phosphorus oxychloride (15 ml.) on the steam-bath for 3 hours. No darkening occurred. After hydrolysis of the phosphorus oxychloride in water (100 ml.), the mixture was heated on the steam-bath for 1 hour to complete the hydrolysis of the *O*-acetyl linkage. The white solid *oxazole* was filtered off and crystallised from aqueous ethanol, to give white crystals, m. p. 211—213° (3·6 g., 80%) (Found: C, 39·4; H, 2·6; I, 46·4. $C_{18}H_{15}O_3NI_2$ requires C, 39·5; H, 2·8; I, 46·4%).

4-[4′-(4″-*Hydroxy*-3″-*sulphophenoxy*)-3′ : 5′-*di-iodobenzyl*]-2 : 5-*dimethyloxazole* (IV; X = SO_3H, Y = H).—The ketone (5 g.) was dissolved in sulphuric acid (5 ml.) at *ca.* 40°, and the solution was set aside for 3 hours. On its being poured into water (40 ml.), a brown oil was precipitated, which solidified slowly when heated on a steam-bath. The nearly white *acid* was crystallised twice from aqueous ethanol, and then melted at 222°, sintering from 177° (Found: I, 40·7; S, 5·4; $C_{18}H_{15}O_6NSI_2$ requires I, 40·5; S, 5·1%).

4-[4′-(4″-*Acetoxy*-3″ : 5″-*di-iodophenoxy*)-3′ : 5′-*di-iodobenzyl*]-2 : 5-*dimethyloxazole*.—DL-3-Acetamido-4-[4′-(4″-acetoxy-3″ : 5″-di-iodophenoxy)-3′ : 5′-di-iodophenyl]butan-2-one (5 g.), dissolved in phosphorus oxychloride (15 ml.), was heated on the steam-bath for 3 hours. The phosphorus oxychloride was hydrolysed in water (100 ml.), and the mixture heated on the steam-

bath for 1 hour. When the solid product was dissolved in ethanol (200 ml.) and concentrated to 20 ml., a little tar was precipitated. The clear liquid was decanted and set aside till crystallisation occurred. The *oxazole* formed nearly white crystals, m. p. 209—211°, sintering at 195° (2·2 g., 48%) (Found: C, 28·6; H, 2·4; I, 59·6. $C_{20}H_{15}O_4NI_4$ requires C, 28·6; H, 1·8; I, 60·3%).

4-[4′-(4″-*Hydroxy*-3″ : 5″-*di-iodophenoxy*)-3′ : 5′-*di-iodobenzyl*]-2 : 5-*dimethyloxazole* (IV; X = Y = I).—Iodine [1·94 ml. of solution in excess of aqueous potassium iodide; 245 g. of iodine per l. (4 atoms)] was added dropwise with stirring to a solution of the di-iodo-compound in 20% ethylamine solution (5 ml.). A pale yellow solid crystallised. The mixture was diluted with water and acidified. The very pale yellow solid that was filtered off crystallised poorly from most solvents. In acetic acid it became oily and dissolved: crystals then separated on scratching. Recrystallisation from acetic acid gave almost colourless crystals of the *tetraiodo*-compound, m. p. 182—183° (decomp.), depressed by the preceding compound (Found: C, 27·6; H, 1·9; I, 61·4. $C_{18}H_{13}O_3NI_4.\frac{1}{2}C_2H_4O_2$ requires C, 27·5; H, 1·8; I, 61·2%). Recrystallisation then from alcohol gave crystals, m. p. 197—199° (decomp.) (Found: C, 28·7; H, 2·2; N, 1·7. $C_{18}H_{13}O_3NI_4.C_2H_6O$ requires C, 28·4; H, 2·3; N, 1·7%).

4-(4-*Benzyloxy*-3 : 5-*di-iodobenzyl*)-2 : 5-*dimethyloxazole* (III; R = CH_2Ph).—The related hydroxy-compound (2 g.) was dissolved in dry ethanol (50 ml.) containing sodium (0·1 g., 1 atom). Benzyl chloride (0·5 ml., 1 mol.) was added and the solution was heated under reflux for 4 hours. The precipitated sodium chloride was removed by filtration, and the solution taken to dryness *in vacuo*. The gum was extracted with warm *cyclo*hexane from which the *ether* crystallised as fine white needles of m. p. 98—99° (1·32 g., 55%) (Found: C, 41·6; H, 3·0; I, 47·2. $C_{19}H_{17}O_2NI_2$ requires C, 41·8; H, 3·1; I, 46·6%).

DL-3-*Acetamido*-4-(4-*benzyloxy*-3 : 5-*di-iodophenyl*)*butan*-2-*one* (I; R = CH_2Ph).—The hydroxy-compound (2 g.) was dissolved in ethyl methyl ketone (50 ml.); benzyl chloride (0·6 ml., 1·1 mols.) and potassium carbonate (1 g., *ca.* 3½ equivs.) were added and the solution was refluxed for 3 hours. The inorganic material was removed by filtration and the solvent removed *in vacuo*. Crystallisation of the gum from ethanol yielded the *ether* as white needles, m. p. 177—178° (1·4 g., 58%) (Found: C, 40·7; H, 3·6; I, 45·6. $C_{19}H_{19}O_3NI_2$ requires C, 40·5; H, 3·4; I, 45·1%). The substance was insoluble in alkali and gave a negative Kendall test.

3 : 5-*Di-iodo*-4-p-*methoxyphenoxycinnamic Acid* (V; R = Me, X = H).—3 : 5-Di-iodo-L-thyronine (50 g.) was dissolved in water (180 ml.) containing sodium hydroxide (8 g.) and stirred while methyl sulphate was added slowly until the pH was about 5 (*ca.* 9 ml.). Sodium hydroxide solution (40%; 15 ml.) was added and methyl sulphate (*ca.* 18 ml.) until the pH was again about 5. Much solid was precipitated. More sodium hydroxide (40%; 18 ml.) was added, followed by methyl sulphate (36 ml.), and the mixture was heated on the steam-bath for 1 hour. A brown oil was precipitated, the pH of the supernatant fluid being 5. A large excess of sodium hydroxide (40%; 80 ml.) was finally introduced and the mixture heated on the steam-bath for 3 hours. The mixture at the end of this period was a thick sludge of fine white needles in a brownish liquid and there was very little smell of trimethylamine.

The needles of sodium salt were filtered off and stirred with 5N-hydrochloric acid to generate the free acid as very fine needles, m. p. 250—252° (46·6 g., 94%). After recrystallisation from a large bulk of ethanol the prisms melted at 253—255° (Found: C, 36·6; H, 2·6; I, 48·3. Calc. for $C_{16}H_{12}O_4I_2$: C, 36·8; H, 2·3; I, 48·6%).

3 : 5-*Di-iodo*-4-(3 : 5-*di-iodo*-4-*methoxyphenoxy*)*cinnamic Acid* (V; R = Me, X = I).—Starting with L-thyroxine a similar process to the above yielded the required compound. In order to dissolve the starting material, equal quantities of ethanol and water were used as solvent. White crystals, m. p. 292—300° (some decomp.), were obtained from aqueous dioxan (47 g. from 50 g.; 94%) (Found: I, 64·9. Calc. for $C_{16}H_{10}O_4I_4$: I, 65·6%).

4-p-*Hydroxyphenoxy*-3 : 5-*di-iodocinnamic Acid* (V; R = X = H).—The foregoing methoxy-acid (10 g.) was dissolved in a mixture of acetic acid (200 ml.) and hydriodic acid (57%; 30 ml.) and the whole refluxed for 2 hours. Some crystalline solid which came out of solution during the heating was filtered off next morning. The crystals were nearly colourless after being washed with acetic acid, and melted at 290—300° (decomp.) (7·2 g., 73%). Crystallisation from aqueous dioxan formed white needles, m. p. 295—296° with some decomposition (Found: C, 35·3; H, 2·2; I, 49·2. Calc. for $C_{15}H_{10}O_4I_2$: C, 35·4; H, 2·0; I, 50·0%).

4-(4-*Hydroxy*-3 : 5-*di-iodophenoxy*)-3 : 5-*di-iodocinnamic Acid* (V; R = H, X = I).—The di-iodo-acid (2 g.) was dissolved in ethylamine solution (16% in water; 60 ml.) which was stirred during the addition, in 5 minutes, of iodine solution (1·9N in excess of sodium iodide; 2·3 ml., 4·4 atoms). Stirring was continued for 1 hour during which the product crystallised.

This was filtered off and stirred with 5N-hydrochloric acid to decompose the ethylamine salt. Crystallisation from a large bulk of acetic acid yielded nearly colourless needles, which finally decomposed at 270°, beginning to lose iodine at 255° (2·0 g., 66%) (Found: C, 24·0; H, 1·35; I, 67·5. Calc. for $C_{15}H_8O_4I_4$: C, 23·7; H, 1·1; I, 66·8%).

Reaction of 3 : 5-*Di-iodo*-4-p-*methoxyphenoxycinnamic Acid with Hydroxylamine.*—Hydroxylamine hydrochloride (3·66 g., 2·2 mols.) in water (7 c.c.) was added to a solution of sodium (1·2 g.; 2·2 atoms) in alcohol (100 c.c.), and the flask was washed with alcohol (5 c.c.) which was also added. The iodocinnamic acid (12·5 g., 1 mol.) and dioxan (30 c.c.) were added to the solution of hydroxylamine, from which the precipitated sodium chloride had been filtered off. A clear solution was obtained on boiling. After about 5 hours' boiling fine crystals of β-*amino*-β-(3 : 5-*di-iodo*-4-p-*methoxyphenoxyphenyl*)*propionic acid* began to separate. After 24 hours' boiling the mixture was cooled and the crystals of β-amino-acid (3·2 g., 25%) were filtered off and washed with water and alcohol. They melted with decomposition at 228—230°. Recrystallisation from pyridine raised the m. p. to 230—231°, with evolution of ammonia. The clear melt recrystallised at about 220° to fine needles of the corresponding cinnamic acid (V; R = Me, X = H), which did not completely remelt till 245° (Found: C, 35·7; H, 3·0; I, 47·2. $C_{16}H_{15}O_4NI_2$ requires C, 35·65; H, 2·8; I, 47·1%).

The β-amino-acid (0·6 g.) was dissolved in N-sodium hydroxide (10 c.c.), and acetic anhydride (0·6 c.c.) was added to the suspension of sodium salt that separated. Enough alkali was added at the same time to keep the solution alkaline. The clear solution was then acidified, and the precipitated β-*acetamido-acid* recrystallised from aqueous acetic acid. The fine colourless crystals sintered from 210° and melted at 248—251° (Found: C, 36·9; H, 2·9; I, 44·2. $C_{18}H_{17}O_5NI_2$ requires C, 37·2; H, 2·8; I, 43·7%)

After ¾ hour's boiling a solution of β-amino-acid (0·25 g.) in acetic acid (2 c.c.) and hydriodic acid (1 c.c.) was cooled, diluted with water, and neutralised with ammonia. The very pale yellow precipitate (0·22 g.) was filtered off and recrystallised from aqueous acetic acid as small rosettes of needles, m. p. (alone and mixed with 4-*p*-hydroxyphenoxy-3 : 5-di-iodocinnamic acid) 295° (decomp.), beginning to sinter at 260°.

3 : 5-*Di-iodo*-4-p-*methoxyphenoxyacetophenone Oxime.*—The filtrate after removal of the β-amino-acid from the reaction mixture was poured into water (2 l.) and twice extracted with chloroform, which was then washed with N-sodium carbonate and water. The residue remaining after evaporation of the chloroform was recrystallised from toluene–light petroleum (b. p. 100—120°), to give the *oxime* (3·55 g., 36%), m. p. 179—181° after sintering from 175°. After two more crystallisations from toluene–light petroleum (charcoal) and one from methyl cyanide, colourless blades (1·8 g.) were obtained, m. p. 183—184° after sintering from 180° (Found: C, 35·8; H, 2·8; I, 49·5. $C_{15}H_{13}O_3NI_2$ requires C, 35·4; H, 2·6; I, 49·8%).

The oxime (0·2 g.) and 2 : 4-dinitrophenylhydrazine (0·08 g., 1 mol.) in alcohol (10 c.c.) and concentrated hydrochloric acid (0·5 c.c.) were boiled. Yellow needles soon began to separate. After ½ hour the mixture was cooled and the 2 : 4-*dinitrophenylhydrazone* (0·25 g., 94%) was filtered off; it formed orange-yellow needles (from toluene), m. p. 225° (Found: N, 8·1; I, 37·0. $C_{21}H_{16}O_6N_4I_2$ requires: N, 8·3; I, 37·65%).

A solution of the oxime (0·5 g.) in alcohol (10 c.c.) and hydrochloric acid (1 c.c.) was boiled for 1 hour. After addition of water the solution deposited crystals of the *ketone* (0·43 g., 89%) on cooling. Recrystallisation from aqueous *iso*propanol and then from aqueous acetic acid gave colourless needles, m. p. 141—142° (Found: C, 36·6; H, 2·3; I, 51·4. $C_{15}H_{12}O_3I_2$ requires C, 36·4; H, 2·45; I, 51·4%).

To this ketone (50 mg.) in dioxan (0·6 c.c.) and 2N-sodium hydroxide (0·5 c.c.), iodine (0·32 c.c.; 245 g./l.; 6 atoms) in potassium iodide solution was added by drops, which were rapidly decolourised. The mixture was kept at about 60° for ½ hour and then diluted with water. A small amount of solid with the characteristic smell of iodoform was filtered off. Acidification of the filtrate produced fine needles of 3 : 5-di-iodo-4-*p*-methoxyphenoxybenzoic acid (40 mg., 80%), which began to sinter at about 200° and finally melted at 234°. An authentic sample (Part I, *J.*, 1949, S 185) showed identical behaviour on being heated alone or mixed.

3 : 5-*Di-iodo*-4-(3 : 5-*di-iodo*-4-*methoxyphenoxy*)*acetophenone.*—(*a*) Hydroxylamine hydrochloride (1·58 g., 2·2 mols.) in water (3 c.c.) and alcohol (2 c.c.) was added to sodium (0·52 g., 2·2 atoms) in alcohol (50 c.c.). After filtration of the sodium chloride the solution was added to 3 : 5-di-iodo-4-(3 : 5-di-iodo-4-methoxyphenoxy)cinnamic acid (8·0 g., 1 mol.) in dioxan (70 c.c.). After 24 hours' boiling the solution was concentrated and filtered from a small amount of gelatinous stuff after dilution with benzene. Evaporation of the solvent left a gum that did not crystallise. It was therefore dissolved in alcohol (150 c.c.) containing hydrochloric acid (7 c.c.)

and 2 : 4-dinitrophenylhydrazine (1·9 g., 0·9 mol.), and boiled for 1 hour. The orange-yellow powder (4·7 g.) was removed from the cooled solution, washed, and dried. It was then dissolved in dioxan (60 c.c.) and benzene (120 c.c.) and chromatographed on activated alumina. The column was developed with dioxan–benzene (1 : 2), the clear yellow solution passing through and leaving greenish, orange, and brown bands on the column. The eluate was washed with water and the resulting benzene solution concentrated to small volume. Light petroleum (b. p. 100—120°) was added to the boiling residue till crystals began to appear. On cooling, the 2 : 4-*dinitrophenylhydrazone* was filtered off (3·9 g., 41%). It separated from chlorobenzene–light petroleum (b. p. 100—120°) in orange crystals m. p. 264—266° (Found : C, 27·4; H, 1·8; I, 54·4. $C_{21}H_{14}O_6N_4I_4$ requires C, 27·2; H, 1·5; I, 54·8%).

A solution of this hydrazone (150 mg.) in acetone (15 c.c.), dioxan (5 c.c.) and hydrochloric acid (0·75 c.c.) was boiled for 2 hours, cooled, and diluted with water till just cloudy. After a few minutes the pale yellow crystals of the *ketone* that had separated were filtered off; they had m. p. 223—226° after sintering from 205° (95 mg., 80%). Further dilution of the mother-liquor with water gave orange fibres of acetone 2 : 4-dinitrophenylhydrazone, m. p. 124—126° (30 mg., 80%). After crystallisation from light petroleum (b. p. 100—120°) the pale yellow needles of ketone sintered at 220° and melted at 224—226° (Found : C, 24·6; H, 1·5; I, 68·4. $C_{15}H_{10}O_3I_4$ requires C, 24·1; H, 1·3; I, 68·1%). After chromatography on alumina the ketone formed colourless blades of unchanged m. p.

(*b*) The cinnamic acid (7·1 g.) was boiled for 24 hours in a solution of hydroxylamine, made from the hydrochloride (1·40 g.) and sodium (0·46 g.), in alcohol (40 c.c.) and dioxan (60 c.c.) as before. After filtration from a little sludge the solution was poured into water, which was twice extracted with benzene. Evaporation of the solvent left a residue not easily recrystallised. So it was dissolved again in benzene and run down an alumina column. The first fractions separated from benzene–light petroleum (b. p. 100—120°) in rosettes of colourless blades (1·8 g., 26%), m. p. 220—224° after sintering from 216°, unchanged when mixed with ketone made from the 2 : 4-dinitrophenylhydrazone.

DL-3 : 5-*Di-iodo*-β-*thyronine*.—To 4-*p*-hydroxyphenoxy-3 : 5-di-iodocinnamic acid (5·0 g.) in dioxan (40 ml.) was added a solution of hydroxylamine, made from the hydrochloride (1·51 g., 2·2 mols.) in water (2 ml.) and alcohol (10 ml.) and sodium (0·50 g., 2·2 atoms) in alcohol (25 ml.). Having been boiled for 24 hours the mixture was filtered and the white solid (0·95 g.) was recrystallised from 50% alcohol. The resulting 3 : 5-*di-iodo*-β-*thyronine* sintered at 230° and melted with decomposition at 303° (Found : C, 34·5; H, 2·6; N, 2·8; I, 48·3. $C_{15}H_{13}O_4NI_2$ requires C, 34·3; H, 2·5; N, 2·7; I, 48·4%).

DL-β-*Thyroxine*.—3 : 5-Di-iodo-β-thyronine (0·32 g.) was dissolved by gentle warming in 33% ethylamine (4 ml.) and water (8 ml.). A solution of iodine (1·0 ml. of 2·76% : 4·4 atoms) in excess of aqueous potassium iodide was then added dropwise. After ½ hour the pH was brought to 6 with dilute acetic acid. The sticky brown precipitate solidified and was then decolourised with sodium hydrogen sulphite solution. It was dissolved in a large volume of methanol, which was filtered and concentrated. On cooling, β-*thyroxine* separated, having m. p. 211° (decomp.) (Found : N, 1·6; I, 65·7. $C_{15}H_{11}O_4NI_4$ requires N, 1·8; I, 65·4%).

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151. *The Action of Ionizing Radiations and of Radiomimetic Substances on Deoxyribonucleic Acid. Part V.* Some Experiments on the Action of X-Rays and Free Radicals.*

By B. E. Conway and J. A. V. Butler.

Experiments have been made to determine the nature of the agent which causes the slow continued change of viscosity of thymus deoxyribonucleic acid after irradiation with *X*-rays in oxygen-containing solutions. Although the change resembles that brought about by hydrogen peroxide when suitably activated, the actual amount of hydrogen peroxide formed is too small to account for the phenomenon. It is suggested that the initial agent is the radical HO_2.

When deoxyribonucleic acid solutions are irradiated with *X*-rays, the immediate effect of the irradiation is followed by a slow fall of viscosity which continues for many hours (Taylor, Greenstein, and Hollaender, *Biochem. Arch.*, 1948, **16**, 19). It was shown (Part II, *J.*, 1950, 3418) that this " after-effect " does not occur if the irradiation is carried out in oxygen-free solutions. The effect was therefore ascribed to the reaction of a primary product of the radiation with molecular oxygen. The most likely product of this reaction appeared to be the radical HO_2, formed by $H + O_2 \longrightarrow HO_2$, which, it was suggested, could then react with nucleic acid forming a compound of a peroxidic nature, which slowly decomposes giving rise to the observed loss of viscosity. There are two distinct problems: (*a*) the nature of the product which causes the effect; (*b*) its action on the nucleic acid. In this paper we report experiments designed to establish more fully the nature of the agent, and particularly to distinguish the action observed from that of hydrogen peroxide. It is well known that hydrogen peroxide is formed by the *X*-irradiation of pure water in the presence of oxygen (Bonet-Maury and Lefort, *Nature*, 1948, **162**, 381, *J. Chim. phys.*, 1950, **47**, 624; Lefort, *ibid.*, p. 624, 776; Gray, *Progress in Biophysics*, Vol. II, 1951) by reactions such as $H + O_2 \longrightarrow HO_2$; $HO_2 + H \longrightarrow H_2O_2$; $2HO_2 \longrightarrow H_2O_2 + O_2$. The effect of added substances is complex. Substances which can react with HO_2 will decrease the yield of hydrogen peroxide, and it has been suggested (Allen, *J. Phys. Coll. Chem.*, 1948, **52**, 473) that reducing agents may increase it.

It was found (Part II, *loc. cit.*) that the effect of added hydrogen peroxide on nucleic acid was complicated in that some samples were degraded and others not. Since (i) samples of nucleic acid which are not sensitive to hydrogen peroxide can be made so by addition of small quantities (10^{-5}M) of ferrous salts, and (ii) samples which are sensitive can be made less sensitive by reprecipitation from aqueous solution by alcohol, it was concluded that hydrogen peroxide has no apparent effect on purified nucleic acid but that small quantities of ferrous salt have an activating effect. It has been found that other reducing agents, such as ascorbic acid and cysteine, are effective in this way (see Fig. 1).

It has also been found (see Fig. 2) that a sample of nucleic acid which is not affected by added hydrogen peroxide still shows the " after-effect." It might perhaps be argued that the added hydrogen peroxide contains an inhibitor, while that formed by the action of *X*-rays does not. However, since the action of hydrogen peroxide on different samples of nucleic acid, some sensitive and some not, is not changed by the distillations, it was concluded that the presence of an inhibitor was not a determining factor.

It is also possible that the action of *X*-rays on the nucleic acid produces an activating agent, which is capable of initiating the decomposition of hydrogen peroxide. There is evidence that this is the case (see Fig. 3), since hydrogen peroxide added to an insensitive nucleic acid preparation, soon after the finish of an irradiation in the absence of oxygen, is able to produce a change similar to the " after-effect." It is to be noted that when the hydrogen peroxide is not added until 24 hours after the finish of the irradiation this effect

* Part IV, *J.*, 1952, 626.

was not observed. The activating agent formed by *X*-rays thus disappears when the solution is kept.

It is evident from this experiment that hydrogen peroxide, if it were formed in the *X*-irradiation in sufficient amount, would be capable of causing the " after effect." The con-

FIG. 1.

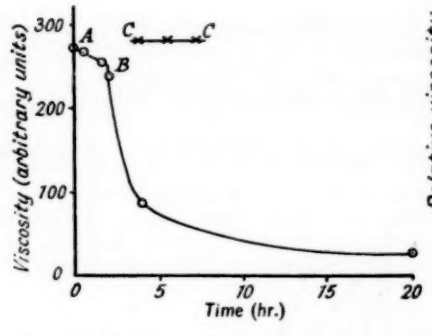


FIG. 2.

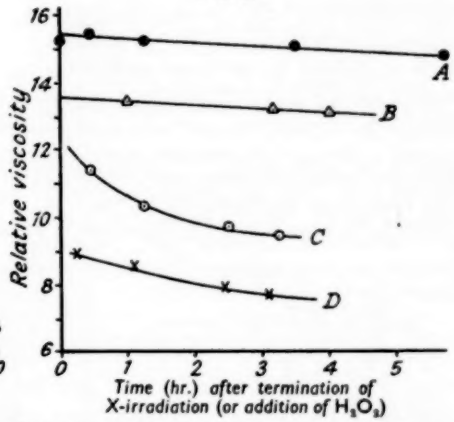


FIG. 1. *Effect of ascorbic acid* (10^{-3}M) *on the hydrogen peroxide* (5×10^{-3}M) *degradation of thymonucleic acid in* 0·1N-*sodium hydrogen carbonate.*

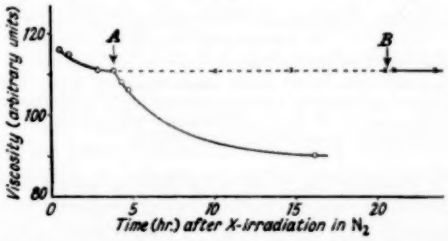
AB shows action of hydrogen peroxide alone; at *B* the ascorbic acid was added; *CC* shows effect of ascorbic acid without hydrogen peroxide.

FIG. 2. *Showing* (1) *that the " after-effect " still occurs with a preparation not directly sensitive to hydrogen peroxide ;* (2) *that the primary effect of* X-*irradiation is increased in the presence of added hydrogen peroxide.*

A, 10^{-3}M-H_2O_2; *T.N.A. is insensitive.* *C*, 7000 r. X-*irradiation in* O_2.
B, 7000 r. X-*irradiation in* N_2. *D*, 7000 r. ,, *in* $O_2 + 3 \times 10^{-3}$M-H_2O_2.

centration required to produce the observed effects is of the order of 10^{-3}M. The table on p. 836 shows the concentrations of hydrogen peroxide formed with *X*-ray doses of the order used in the experiments, both in oxygenated water and in the presence of oxygenated nucleic acid solution. It can be seen that the concentrations are smaller, by a factor

FIG. 3. *Effect of hydrogen peroxide on* X-*irradiated thymonucleic acid after two periods of time.*



A, H_2O_2 *added* (10^{-3} *mole/l.*). *B*, H_2O_2 *added* (10^{-3} *mole/l.*) *after* 20 *hours : no effect.*

of at least 30, than those which would be required to produce the " after-effect " if hydrogen peroxide were the active agent. The figures for water are in reasonable agreement with the observations by Bonet-Maury and Lefort (*loc. cit.*).

A direct comparison was made by determining (*a*) the concentration of hydrogen peroxide formed in the *X*-irradiation (7000 r.) of an oxygenated solution of nucleic acid and (*b*) the effect of this concentration (*ca.* 4×10^{-5}M) when added to the same solution

irradiated in nitrogen with the same dose of *X*-rays. The change of viscosity produced by the latter was only 2—3% in 5 hours, whereas the " after-effect " under these conditions is a 20—50% change.

Formation of hydrogen peroxide (in moles/l. × 10^3) in oxygenated water and nucleic acid solutions.

Concn. of nucleic acid (%)		0	0·005	0·01	0·05	0·1
X-Ray dose (r.) (206 r./min.)	3 000	0·1	0·04	0·06	0·04	0·04
	10 000	0·08	0·04	0·04	0·04	0·06
	20 000	0·06	0·04	0·04	0·04	0·06

It might be argued that, when nucleic acid is present, larger amounts of hydrogen peroxide are actively formed which become adsorbed on the nucleic acid. If this were the case a similar phenomenon would be expected with added hydrogen peroxide, but when this is added to nucleic acid solutions at a concentration of 10^{-3}M, the amount adsorbed is not more than equivalent to 10^{-4}M.

Further evidence that the degradation of nucleic acid is not caused by an agent which

FIG. 4.

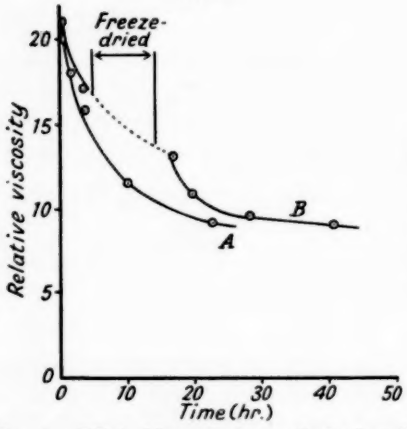


FIG. 5.

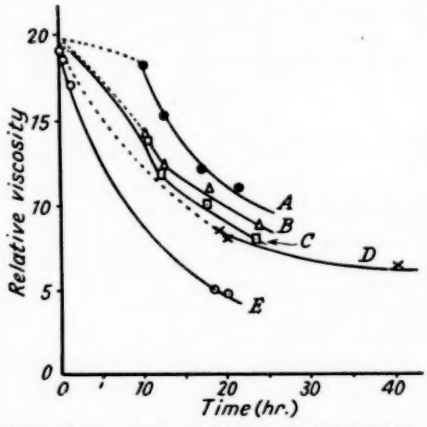


FIG. 4. *Effect of freeze-drying on the " after-effect " in thymonucleic solution X-irradiated (7000 r.) in oxygen.*

A, Control, not freeze-dried.
B, Freeze-dried for period shown and reconstituted to same concentration with water.

FIG. 5. *Effect of freeze-drying of thymonucleic acid treated with hydrogen peroxide under various conditions.*

A, Frozen at −20° but not dried.
B, Freeze-dried for 10 hr. (99% water removed), reconstituted.
C, Freeze-dried for 2 hr. (60% water removed), reconstituted.
D, Freeze-dried for 20 hr. (100% water removed), reconstituted.
E, Control at 25° without freezing or drying.

remains in the solution is given by experiments in which the solution was frozen as soon as possible after the completion of the irradiation and the volatile components were removed by sublimation in a freeze-drying apparatus. It was found (Fig. 4) that (*a*) after the substance had been kept for a limited time in the solid state and then redissolved, the degradation process continued, (*b*) degradation also appeared to occur during the time the substance was in the solid and in the dried solution.

These observations support the view that the slow degradation process produced both by *X*-rays in oxygenated solutions and by activated hydrogen peroxide is caused by an agent which has become attached to the nucleic acid. The radical HO_2 is indicated because it is formed both by the action of a primary product of *X*-rays on molecular oxygen and by the action of ferrous ions (and possibly other reducing agents) on hydrogen peroxide,

as in the following scheme (Haber and Weiss, *Proc. Roy. Soc.*, *A*, 1934, **147**, 332; Humphrey and Weiss, *Nature*, 1949, **163**, 691; Barb, Baxendale, George, and Hargrave, *ibid.*, p. 692):

$$H_2O_2 + Fe^{++} \longrightarrow OH + Fe^{+++} + OH^- \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad (1)$$
$$H_2O_2 + OH \longrightarrow H_2O + HO_2 \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad (2)$$
$$HO_2 + H_2O_2 \longrightarrow O_2 + H_2O + OH \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad (3)$$
$$Fe^{+++} + HO_2^- \longrightarrow Fe^{++} + HO_2 \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad (4)$$

With small concentrations of ferrous ions, a chain reaction involving (2) and (3), initiated by (1), can occur, but it is evident that if a substance which removes HO_2 is present, (3) will be inhibited and the continuation of the formation of HO_2 requires the regeneration of Fe^{++} by some such process as (4).

An experiment was also made to find if irradiation with *X*-rays increased the "after-effect" (see Fig. 2) when hydrogen peroxide was present. It was found that the *primary* effect of the *X*-rays is greatly increased, *e.g.*, 1000 r. in the presence of 3×10^{-3}M-hydrogen peroxide has a greater effect than 7000 r. in nitrogen. There is some "after-effect," but not more than could be attributed to traces of oxygen formed from the hydrogen peroxide. It therefore appears likely that the *X*-irradiation of hydrogen peroxide gives rise mainly to OH radicals, which produce a primary effect, and that the decomposition as $H_2O_2 \longrightarrow H + HO_2$ is not sufficient to produce a large secondary effect.

Experimental

The materials and methods of measurements were similar to those described in Part II (*loc. cit.*).

Determination of Hydrogen Peroxide.—The peroxide formed during the *X*-irradiation of the oxygenated nucleic acid solution was determined colorimetrically with titanic sulphate solution. 1 Ml. of 0·6% aqueous titanic sulphate in 20% aqueous sulphuric acid was added to 1 or 5 ml. of the nucleic acid solution, and the mixture made up to 10 ml. The precipitated nucleic acid was centrifuged off, and the optical density of the solution was measured in a Unicam spectrophotometer at 4300 Å and compared with that obtained with suitable standards. When 5 ml. of nucleic acid with known concentrations of hydrogen peroxide are used, the accuracy is $\pm 2 \times 10^{-5}$M-H_2O_2.

Effect of Freeze-drying.—*X*-Irradiated solutions in oxygen were freeze-dried as quickly as possible after the irradiation. In the similar experiments carried out in the presence of hydrogen peroxide and ferrous salts the solution was frozen as soon as possible after the addition of the reagent. After being in the dry state for 16—20 hours, the solution was reconstituted, and a much degraded product was obtained. This could have been obtained either by the reaction's occurring in the dry frozen state, or as a reaction of hydrogen peroxide accelerated by concentration of the solution, during the actual stages of the freezing. The freezing process only occupies a few seconds. Experiments with hydrogen peroxide solutions showed that no significant concentration occurs during partial freezing or during the evaporation; *i.e.*, the hydrogen peroxide is evaporated at a rate which is at least not greatly different from that of the water. Experiments in which the thymonucleic acid solutions containing hydrogen peroxide were frozen and dried for various times so as to remove different amounts of water, and an experiment in which the solution was merely frozen and remelted after 10 hours indicated that the viscosity-decay curves for the reconstituted solutions from *partly* and *completely dried* solids were largely superimposable (Fig. 5). However, mere freezing of the solution without removal of the water greatly diminishes the rate of change in the solid state.

Temperature Coefficient of the Degradation Process.—It is difficult to deal with the kinetics of the change when the relation between the viscosity and the underlying chemical changes is unknown. The relation $(\eta_{i0} - \eta_{it})/(\eta_{it} - \eta_{i\infty}) = k_2 t$, where η_{i0} and $\eta_{i\infty}$ are the initial and the final viscosity and η_{it} is that at time t, was found to be in good agreement with the observed results in most cases. This relation can be derived on certain assumptions from a second-order law, the initial concentrations of reactants being assumed to be the same. The following values of k_2 were obtained:

Temp.	5°	15°	25°	37°
H_2O_2 + nucleic acid	0·16	0·45	0·92	0·96
X-Irradiation of nucleic acid oxygen (7000 r.)	(3°) 0·073	0·100	0·155	0·58

From these temperature coefficients it can be concluded that in aqueous solution the rate of change at 0° is only about 0·25 of that at 25° and will be still less at the lower temperatures which prevail at least during the early stages of the freeze-drying. It would appear from this that the rates of change observed during the drying process and in the dry state are at least as great as, and possibly greater than, those to be expected in solution at similar temperatures.

Action of Catalase.—Since hydrogen peroxide is decomposed by catalase, it was thought that its effect on nucleic acid containing hydrogen peroxide would be of interest. Catalase alone has no effect on the viscosity of nucleic acid, but catalase and hydrogen peroxide produced an abrupt decrease of viscosity, after which the viscosity remained constant. This is evidence that catalase liberates hydroxyl radicals in its action on hydrogen peroxide, but the amount is relatively small and is insufficient to produce measurable chemical changes, such as can easily be observed in the case of hydroxyl radicals produced by the photochemical decomposition of hydrogen peroxide. The liberation may, however, not be connected with the specific catalase decomposition of hydrogen peroxide, but a consequence of a secondary activation of hydrogen peroxide, caused by catalase acting as a reducing agent and so producing an effect similar to that noted with ascorbic acid (Fig. 1). The addition of catalase to *X*-irradiated nucleic acid in oxygen had very little effect.

Effect of Substances added after the Irradiation.—The effect of oxygen on the results of *X*-irradiation is of considerable importance in radiobiology, since it has been found in a variety of experiments that radiation damage is increased by an increased concentration of oxygen (*e.g.*, Thoday and Read, *Nature*, 1947, **160**, 608; 1949, **163**, 133; Hollaender, Stapleton, and Morton, *ibid.*, 1951, **167**, 103) and is much reduced by exclusion of oxygen (Evans, *Radiobiology*, 1942, **38**, 29). Since oxygen exclusion is difficult to achieve with many living organisms, alternative methods of protection have been sought, *e.g.*, the addition of cysteine or other substances (Patt *et al.*, *Science*, 1949, **110**, 213; *Proc. Soc. Exp. Biol.*, 1950, **73**, 18). To be effective, these substances have to be present during the irradiation. They exert this effect by competing for the primary radicals produced by *X*-rays. It appeared to us that it might be possible to prevent the " after-effect " of nucleic acid by adding *after the irradiation* substances which could reduce or decompose the suggested nucleic acid peroxide, and that this experiment might indicate substances which would be effective *in vivo*. None of the substances added after the irradiation (cysteine, ascorbic acid, ferrous ions, catalase, peroxidase) was effective in preventing the occurrence of the after-effect. On the contrary most of them accelerated it, and it would appear that reaction such as $XO_2H + R \longrightarrow XO\cdot + R(OH)$ may be possible. It is noteworthy in this connection that Kharasch has shown (*Science*, 1951, **113**, 392) that alkoxy-radicals are formed by the action of ferrous ions on alkyl peroxides.

We are indebted to Dr. L. F. Lamerton and Miss E. B. Harriss, Physics Department, Royal Cancer Hospital, for carrying out the irradiations. This investigation has been assisted by grants to the Royal Cancer Hospital and the Chester Beatty Research Institute from the British Empire Cancer Campaign, the Jane Coffin Childs Fund for Medical Research, the Anna Fuller Fund, and the Division of Research Grants of the U.S. Public Health Service.

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152. *The Kinetics of Two Ionic Exchange Reactions of the Methyl Halides in Ethylene Glycol Solution.*

By J. S. MCKINLEY-MCKEE and E. A. MOELWYN-HUGHES.

The reaction between methyl bromide and the iodide ion in ethylene glycol solution has been investigated kinetically, and the results have been compared with those previously obtained for the same reactions in other solvents.

IN this investigation the displacement reactions

$$CH_3Br + I^- \underset{k_4}{\overset{k_3}{\rightleftharpoons}} CH_3I + Br^-$$

have been studied in ethylene glycol as solvent in order to compare the results with those previously determined in water (Moelwyn-Hughes, *J.*, 1938, 779), methyl alcohol (*idem*,

Trans. Faraday Soc., 1939, **35**, 368), and acetone (*idem, ibid.*, 1949, **45**, 167). As in other hydroxylic solvents, the displacement reactions are complicated at higher temperatures by simultaneous reaction with the solvent. The investigation has been here confined to temperatures where the solvolytic changes are negligible.

Experimental

Purification and Some Physicochemical Properties of Ethylene Glycol.—The commercial sample of ethylene glycol used required only one distillation to be of satisfactory purity. The vacuum-distillation unit used for the purification was a Ramsay–Young apparatus, modified by the inclusion of an electrically heated 22" Fenske column packed with single-turn glass helices and equivalent to about 15 theoretical plates. The column head (Human, *J. Soc. Chem. Ind.*, 1949, **68**, 188) had a small hold-up and allowed a reflux ratio of 1 : 10 to be easily set and maintained. The pressure was regulated to $\pm 0{\cdot}1$ mm. and measured on a wide-bore manometer by means of a cathetometer. Two litres were distilled at a time at a pressure of 7—8 mm. of mercury and at a temperature of *ca.* 87·5°. A single controlled distillation gave a liquid of constant refractive index (n_D^{25} 1·4304). Over the range 10—35°, the refractive index of pure ethylene glycol is given by the equation $n_D = 1{\cdot}5131 - 2{\cdot}77 \times 10^{-4}T$, where T is the absolute temperature, according to which $n_D^{20} = 1{\cdot}4318$ (Pukrev, *Trans. Inst. Pure Chem. Reagents*, 1937, **15**, 45, gives 1·4321; Landolt, *Ann. Physik*, 1864, **122**, 547, gives 1·42743).

Densities (d_4^t, g./ml.) and viscosities (η, g. cm.$^{-1}$ sec.$^{-1}$) were determined at 20°, 30°, and 40°, the former being corrected for buoyancy, and the latter for kinetic energy effects according to British Standard Specification 188 (1937). The densities are given by the equation $d_4^t = 1{\cdot}31843 - 0{\cdot}00070t$, which agrees with the results of Riiber, Sorensen, and Thorkelsen (*Ber.*, 1925, **58**, 964) and of Pukrev (*loc. cit.*). The viscosities are reproduced by the equation $\eta = 1{\cdot}500 \times 10^{-4}e^{6885/RT}$ which gives values higher than those of Bingham and Fornwalt (*J. Rheology*, 1930, **1**, 373), but in agreement with those of Fordham (*Research*, 1948, **1**, 336). For the vapour-pressure measurements several temperature readings were taken when equilibrium was established at each pressure. The results are compared in the table with those given by

Vapour pressure of ethylene glycol.

T, °K	358·8	373·9	379·8	386·1	392·6	397·7	406·1
P, mm. obs.	6·8	16·3	22·4	30·6	41·2	54·7	76·9
P, mm. calc.	6·8	16·1	22·1	30·4	41·7	53·0	77·2
T, °K	412·0	418·9	429·5	435·6	450·6	461·7	470·9
P, mm. obs.	98·0	132·0	202·6	244·2	400·7	592·4	773·2
P, mm. calc.	99·4	132·1	198·8	249·0	416·0	590·6	776·7

the equation $\log_{10} P\,(\text{mm.}) = 47{\cdot}5695 - 12{\cdot}485 \log_{10} T - 5325{\cdot}28/T$. The boiling point is found to be 197·43° (Stull, *Ind. Eng. Chem.*, 1947, **39**, 517, gives 197·32°; Gallagher and Hibbert, *J. Amer. Chem. Soc.*, 1937, **59**, 2521, give 197·4°). The molar heat of evaporation (L) varies with temperature according to the equation $L(\text{cal./mole}) = 24\,357 - 12{\cdot}48RT$, being 14 069 cal./mole at the b. p. (Stull, *loc. cit.*, gives 14 013; Gallagher and Hibbert, *loc. cit.*, give 13 633).

Purification of Methyl Bromide.—After a trap-to-trap distillation from solid carbon dioxide to liquid air, a commercial sample of methyl bromide was distilled through a low-temperature fractionating column which was equivalent to about 15 theoretical plates. The column was packed with Fenske helices and surrounded by a vacuum jacket to prevent heat interchange. A still head with a gaseous take-off was employed, a mixture of solid carbon dioxide and alcohol (−78°) being used to condense the methyl bromide. The take-off ratio was 1 : 10, an auxillary condenser and tap enabling this to be controlled. The distillation was carried out smoothly at 40 mm. pressure, and the middle third was collected in a liquid-air condenser. The distillate was stored in a blackened glass receiver connected to the rest of the apparatus through a vacuum-tight bellows needle valve. Bubbling methyl bromide through silver nitrate solution showed that it contained no free acid or halogen, and passage over magnesium perchlorate did not affect its vapour pressure, which at the temperature of melting ice was $662{\cdot}5 \pm 0{\cdot}5$ mm., in good agreement with the result of Egan and Kemp (*J. Amer. Chem. Soc.*, 1938, **60**, 2097), *viz.*, 662·61 mm. Digestion of a weighed amount with excess of potassium hydroxide also showed that the preparation was pure. The solubility of methyl bromide (c) at various partial pressures (p) was obtained by analysing saturated solutions prepared by shaking the vapour with ethylene glycol in a bulb attached to the vacuum-distillation apparatus. The results are shown in the following table.

Solubility of methyl bromide in ethylene glycol at 20°.

p (mm.)	49	105	190	293	492	758
c (moles/l.)	0·050	0·110	0·204	0·326	0·578	0·910
$p/c \times 10^{-2}$	9·80	9·56	9·30	8·98	8·51	8·33

The Solubility of Potassium Iodide and Bromide in Ethylene Glycol.—" AnalaR " Potassium bromide and iodide were recrystallised from water, dried in a vacuum-desiccator, and kept in the dark. For the solubility measurements, saturated solutions were prepared by shaking the dry salts and ethylene glycol in stoppered tubes in a thermostat. From the accompanying

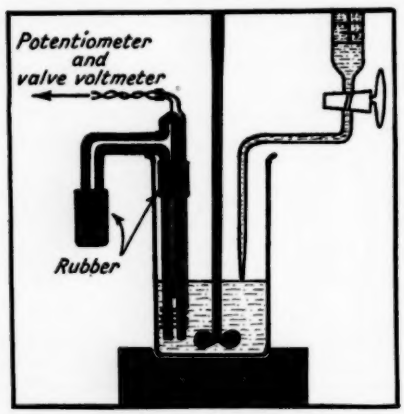
Solubilities (g./l.) of potassium iodide and bromide in ethylene glycol.

	KI		KBr			KI		KBr	
T, °K	(obs.)	(calc.)	(obs.)	(calc.)	T, °K	(obs.)	(calc.)	(obs.)	(calc.)
298·18	467·3	467·4	164·6	164·2	348·18	510·0	510·5	193·2	193·8
320·33	489·8	487·3	176·7	177·4	373·18	527·8	527·8	206·7	206·4

results, it is found that the solubility of the iodide is given by the equation $S = 856{\cdot}3e^{-358{\cdot}7/RT}$, the value at 298·18° K (467·3 g./l.) being lower than Walden's value of 472·3 g./l. (*Z. physikal. Chem.*, 1906, **55**, 683). The solubility of the bromide is given by the equation $S = 511{\cdot}5e^{-672{\cdot}8/RT}$ and is 167·2 g./l. at 303·18° K, which is slightly higher than Trimble's value of 165·9 g./l. (*J. Ind. Eng. Chem.*, 1931, **23**, 165).

Method of Analysis.—Two methods were satisfactory for the analysis of mixtures of bromides and iodides. In the first the sample was split; the iodide was determined by Andrews's method (Moelwyn-Hughes, 1949, *loc. cit.*), and the total halide argentometrically, eosin being used as an adsorption indicator, in the presence of dilute acetic acid, which prevented the precipitation of mixed halide (Kolthoff and van Berk, *Z. anal. Chem.*, 1927, **70**, 396). In the second and more convenient method, the iodide- and bromide-ion concentrations were obtained by a single potentiometric titration with 0·02M-silver nitrate. The electrode system (see Fig.) was a modification of Müller's capillary electrode (Müller, *Z. physikal. Chem.*, 1928, **135**, 102; Stokes, Thesis, Cambridge, 1949), which has the advantages that there is no salt bridge, and that the titrations commence at zero e.m.f. The silver wire electrodes, when prepared by Clark's method (*J.*, 1926, 749), were quite stable, and reached equilibrium rapidly. The e.m.f. was measured on a Cambridge potentiometer, with a valve voltmeter (Garman and Drotz, *Ind. Eng. Chem. Anal.*, 1939, **11**, 398) as a null indicator. From about 2 c.c. before the end-point (indicated by the e.m.f.) to about 2 c.c. after, the silver nitrate solution was added in 0·02-c.c. increments, and the e.m.f. was recorded when steady. The first differences of the e.m.f. were plotted against the titre, symmetrical curves resulting, the mid-point of which gave the end-point of the titration. Following Leibich (" Die potentiometrische Bestimmung von Chlor, Brom und Iod," Diss., Dresden, 1920), 5% of barium nitrate was used in these titrations. Tests with prepared mixtures showed that the method was satisfactory even when the iodide : bromide ratio varied widely (1 : 8 to 8 : 1 by weight).

Capillary electrode system.



Kinetic Procedure.—Solutions of methyl bromide (0·08—0·10M) were prepared in the apparatus previously used to measure its solubility in ethylene glycol. The potassium iodide solutions (0·06—0·20M) were prepared by weight, and dissolved air was pumped out. In carrying out a run, 100 c.c. of iodide solution and 100 c.c. of methyl bromide solution were preheated in the thermostat, mixed, and sucked into a reaction vessel designed so that there was no vapour phase (Moelwyn-Hughes, *Trans. Faraday Soc.*, 1941, **37**, 279). Blank experiments showed that the reactants were unaffected by mercury. As pure ethylene glycol is very hygroscopic, the solutions were protected from the atmosphere at all stages by magnesium perchlorate tubes. After being freed from air they were kept under an atmosphere of nitrogen. There was no evidence of oxidation during a run. Time was reckoned from the moment of

mixing. 10-C.c. samples, removed and analysed at convenient intervals, gave the rate of disappearance of iodide ion and the rate of appearance of bromide ion. For each run three or four samples were sealed off in Pyrex tubes with excess of potassium hydroxide solution, and after overnight digestion at 100°, analysed for inorganic iodide and bromide. The analytical values obtained for the various tubes agreed to within $\pm 0{\cdot}5\%$.

Stationary-state Constants.—Runs at temperatures above 50° showed that there was reaction with the solvent, as in water (Moelwyn-Hughes, 1938, *loc. cit.*). However, at the temperatures

TABLE 1. *Observed and calculated stationary-state concentrations* (m-mole/l.).

T, °K	$[I^-]_0$	$[CH_3Br]_0$	$[Br^-]_s$	$[CH_3I]_s$	$[I^-]_s$	$[CH_3Br]_s$	K_s
288·18	31·28	40·34	27·96	27·96	3·32	12·38	19·02
			(27·96)	(27·96)	(3·32)	(12·38)	(19·0)
288·18	102·50	52·50	50·24	47·24	55·26	2·26	19·00
			49·99	(49·99)	(52·51)	(2·51)	(19·00)
298·18	30·18	40·77	27·25	26·73	3·45	13·52	15·65
			26·81	(26·81)	(3·37)	(13·96)	(15·4)
298·18	30·08	39·78	27·72	26·70	4·15	12·06	14·8
			(26·60)	(26·60)	(3·50)	(13·18)	(15·4)
298·18	49·02	36·80	32·95	31·97	18·05	3·13	15·30
			(32·58)	(32·58)	(16·44)	(4·22)	(15·40)
298·18	49·85	38·50	34·30	33·88	18·20	4·00	16·0
			(33·83)	(33·83)	(16·02)	(4·67)	(15·4)
298·18	101·32	37·72	36·43	35·71	65·61	1·32	15·0
			(36·39)	(36·39)	(64·93)	(1·33)	(15·4)
298·18	104·50	35·40	34·40	32·90	71·60	1·00	15·8
			(34·30)	(34·30)	(70·20)	(1·09)	(15·4)
308·18	33·60	37·31	29·10	26·50	7·10	8·21	13·2
			(27·50)	(27·50)	(6·10)	(9·81)	(12·7)
308·18	28·80	41·40	26·70	25·10	3·70	14·70	12·2
			(25·54)	(25·54)	(3·26)	(15·86)	(12·7)
318·18	30·18	48·76	28·02	26·76	3·42	20·74	10·6
			(27·02)	(27·02)	(3·16)	(21·74)	(10·6)
318·18	29·43	41·91	27·37	25·00	4·43	14·54	10·6
			(25·63)	(25·63)	(3·80)	(16·28)	(10·6)

at which the exchange reactions were studied (288·18—318·18° K) the amounts of organic halide that had reacted with the solvent were negligible, as can be seen from the very slight increase in the $[I^- + Br^-]$ concentration (Table 3). The stationary state constant

$$K_s = [Br^-]_s[CH_3I]_s/[I^-]_s[CH_3Br]_s \simeq k_2/k_4$$

resembles an equilibrium constant, but changes slowly with time. Experimentally, it was obtained by analysis at the end of a run. Table 1 shows the observed and calculated stationary state concentrations obtained for the kinetic runs at the various temperatures. The observed concentration of organic halide is, as expected, generally slightly less than the calculated value.

TABLE 2. *Variation of the stationary-state constant* K_s *with temperature.*

T, °K	288·18	298·18	308·18	318·18
K_s obs.	19·0	15·6	12·7	10·6
K_s calc.	19·0	15·4	12·7	10·6

The equation

$$\log K_s = \bar{2}{\cdot}5931 + 773{\cdot}5/T \text{ or } K_s = 3{\cdot}92 \times 10^{-2}e^{+3539/RT}$$

accounts for the change in K_s. If K_s is treated as an equilibrium constant, then at 298·18° K,

$$\Delta G_s = -RT \ln K_s = -1620 \text{ cal. and } \Delta S_s = (\Delta H_s - \Delta G_s)/T = 17{\cdot}3 \text{ cal./mole-degree}$$

These values are very similar to those obtained for these reactions in methyl alcohol (Moelwyn-Hughes, *loc. cit.*, 1939).

Velocity Coefficients.—As the concentrations used in these experiments did not exceed 0·1M, the limit of solubility of the potassium halides was not approached. The bimolecular constants for the opposing reactions

$$\underset{(a-x)}{CH_3Br} + \underset{(a-x)}{I^-} \underset{k_4}{\overset{k_2}{\rightleftharpoons}} \underset{x}{CH_3I} + \underset{x}{Br^-}$$

were calculated from the relation

$$dx/dt = k_2(a - x)(b - x) - k_4x^2$$

which on integration gives (see Moelwyn-Hughes, *loc. cit.*, 1938; "Physical Chemistry," Cambridge, 1950, p. 523)

$$k_2 = \frac{1}{2(1 - K)Bt} \cdot \ln\left\{\frac{1 - x/(A + B)}{1 - x/(A - B)}\right\}$$

$$x = \frac{ab}{1 - K}\left\{A + B\coth\left[(k_2 - k_4)Bt\right]\right\}^{-1}$$

where $K = 1/K_s = k_4/k_2$, $A = (a + b)/2(1 - K)$, $B = [(a - b)^2 + 4Kab]^{\frac{1}{2}}/2(1 - K)$

Table 3 gives the results of a typical experiment. In all experiments k_2 was calculated for each individual reading and obtained graphically by plotting $\log\left\{\frac{1 - x/(A + B)}{1 - x/(A - B)}\right\}$ against t. The latter method afforded a check on the zero of time. k_4 was calculated from the relation $k_4 = k_2/K_s$. A three-fold increase in the concentration of potassium iodide at 298·18° K (Table 4) results in a decrease in the velocity coefficient, as found in acetone (Moelwyn-Hughes, *loc. cit.*, 1949).

TABLE 3. $[CH_3Br]_0 = 0{\cdot}04034$M; $[I^-]_0 = 0{\cdot}03128$M; $T = 288{\cdot}18°$ K.

			[Br⁻]						[Br⁻]		
t, min.	[I⁻]	[I⁻ + Br⁻] (m-mole/l.)	(obs.)	(calc.)	10^3k_2 (l./mole-sec.)	t, min.	[I⁻]	[I⁻ + Br⁻] (m-mole/l.)	(obs.)	(calc.)	10^3k_2 (l./mole-sec.)
0	31·28	—	0	0	—	180	20·58	31·26	10·68	10·69	1·13
15	30·04	31·25	1·22	1·23	1·12	240	18·35	31·26	12·91	12·91	1·13
40	28·02	31·22	3·20	3·21	1·13	320	15·90	—	15·36	15·28	1·14
82	25·40	31·24	5·84	5·82	1·13	501	12·08	31·27	19·19	19·40	1·15
120	23·37	—	7·87	7·93	1·12	∞	3·32	31·28	27·96	27·96	—

$K_s = 19{\cdot}0$; $k_2 = 1{\cdot}13 \times 10^{-3}$ l./mole-sec.; $k_4 = 0{\cdot}60 \times 10^{-4}$ l./mole-sec.

TABLE 4. *Influence of concentration and temperature on the velocity coefficients.*

T, °K	$[I^-]_0$ (m.-moles/l.)	$[CH_3Br]_0$	$k_2 \times 10^3$ (l./mole-sec.)	$k_4 \times 10^4$	T, °K	$[I^-]_0$ (m.-moles/l.)	$[CH_3Br]_0$	$k_2 \times 10^3$ (l./mole-sec.)	$k_4 \times 10^4$
288·18	31·28	40·34	1·13	0·60	298·18	101·32	37·72	2·90	1·88
,,	102·50	52·50	1·12	0·59	,,	104·50	35·40	2·91	1·89
298·18	30·18	40·77	3·10	2·01	308·18	33·60	37·31	8·80	6·93
,,	30·08	39·78	3·45	2·24	,,	28·80	41·40	8·71	6·86
,,	49·02	36·80	3·30	2·14	318·18	30·18	48·76	20·98	19·80
,,	49·85	38·50	3·35	2·18	,,	29·43	41·91	21·70	20·47

TABLE 5. *Influence of temperature on the velocity coefficients.*

$[I^-]_0 \simeq 0{\cdot}03$M. $[CH_3Br]_0 \simeq 0{\cdot}04$M.

	$k_2 \times 10^3$		$k_4 \times 10^4$			$k_2 \times 10^3$		$k_4 \times 10^4$	
	(obs.)	(calc.)	(obs.)	(calc.)		(obs.)	(calc.)	(obs.)	(calc.)
T, °K.	(l./mole-sec.)				T, °K.	(l./mole-sec.)			
288·18	1·13	1·14	0·60	0·60	308·18	8·76	8·70	6·90	6·85
298·18	3·28	3·26	2·13	2·12	318·18	21·70	21·84	20·47	20·58

Table 5 shows the effect of temperature on the velocity coefficients when constant concentrations of methyl bromide and potassium iodide are used. The equations

$$k_2 = 4{\cdot}56 \times 10^{10}e^{-17\,927 \pm 260/RT} \quad \text{and} \quad k_4 = 1{\cdot}08 \times 10^{12}e^{-21\,417 \pm 220/RT}$$

obtained by the method of least squares reproduce the experimental velocity coefficients. Owing to the nature of the reactions the results are neither extensive nor accurate enough to show whether the activation energy changes with temperature.

DISCUSSION

In the following table the velocity constants and Arrhenius constants, A and E_A, obtained in this work are compared with those found in acetone, methyl alcohol, and water

(Moelwyn-Hughes, *loc. cit.*, 1949). The rates in ethylene glycol solution are seen to be about three times as fast as in methyl alcohol and about four times as fast as in water. A similarity between alcohols and glycols has also been found in the decarboxylation of

Influence of the solvent on the kinetics of reactions between halogen ions and methyl halides.

	$CH_3Br + I^- \longrightarrow CH_3I + Br^-$			$CH_3I + Br^- \longrightarrow CH_3Br + I^-$		
Solvent	$10^4k_{298.1}$ (l./mole-sec.)	$10^{10}A$	E_A (cal./mole)	Solvent	$10^4k_{298.1}$ (l./mole-sec.)	$10^{10}A$	E_A (cal./mole)
Acetone ...	3550	1·15	14 340 ± 1200	Acetone...	4090	28·3	16 150 ± 1500
Glycol ...	32·6	4·56	17 927 ± 258	Glycol ...	2·12	108·0	21 417 ± 220
Methanol	9·42	2·26	18 250 ± 250	Methanol	0·798	39·1	21 400 ± 400
Water ...	6·84	1·68	18 250 ± 130	Water ...	0·461	1·08	19 620 ± 440

sodium trichloroacetate (Auerbach, Verhoek, and Henne, *J. Amer. Chem. Soc.*, 1950, **72**, 299) which proceeds at almost equal rates in ethylene glycol (E_A = 31 600 cal./mole) and in ethyl alcohol (E_A = 31 800 cal./mole).

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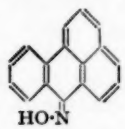
153. *Reactivity of the Carbonyl Group in* meso*Benzanthrone.*

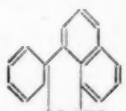
By Neil Campbell and A. A. Woodham.

*meso*Benzanthrone slowly forms an oxime which undergoes the Beckmann transformation to give a lactam whose structure has been established by synthesis and oxidation. Reduction with the Meerwein–Ponndorf reagent unexpectedly gives *meso*benzanthrene and provides the best method for the synthesis of this hydrocarbon. *meso*Benzanthrone with phosphorus pentachloride and phosphorus oxychloride gives dinuclear products, and with certain acids forms oxonium salts which have been examined by Kofler's " contact method."

Although *meso*benzanthrone undoubtedly contains a carbonyl group, no effort has been made, so far as we are aware, to prepare the oxime, etc. We have, therefore, studied the oximation of *meso*benzanthrone and found that the carbonyl group reacted very sluggishly. Heating *meso*benzanthrone with hydroxylamine hydrochloride in pyridine for 8 hours gave little or no oxime, but extending the period to 20 and 70 hours gave yields of 30—50% and 80% respectively of an oxime (I). The oxime of 3-chloro*meso*benzanthrone was prepared similarly.

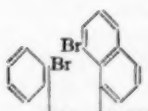


(I)



(II)

(III)



(IV)

The oxime (I) underwent the Beckmann rearrangement when treated with phosphorus pentachloride and phosphorus oxychloride (cf. Moore and Huntress, *J. Amer. Chem. Soc.*, 1927, **49**, 2621) to give a lactam (II) and a chloro-derivative which must be the chloro-derivative of either (I) or (II) (cf. Moore and Huntress, *loc. cit.*). The lactam is completely resistant to hydrolysis and thereby resembles the analogous phenanthridone.

Efforts were made to synthesise the lactam, or its isomer in which the NH and CO groups are interchanged, by the pyrolytic ring closure of *N*-benzoyl-α-naphthylamine (III*a*) and of 1-naphthanilide (III*b*) (cf. Meyer and Hofmann, *Monatsh.*, 1916, **37**, 681). The former gave a small quantity of a substance which is certainly not a *meso*benzanthrone

lactam, and the latter yielded only naphthalene and unchanged material. The method was, therefore, abandoned in favour of the intramolecular condensations of the *o*-bromoanilide (IV*a*) of 8-bromo-1-naphthoic acid and 8-bromo-*N*-*o*-bromobenzoyl-1-naphthylamine (IV*b*). The first compound gave three products: *N*-phenylnaphthastyril, formed by the interaction of the naphthalene-bromine atom with the amino-group and subsequent dehalogenation; a substance of low m. p., high solubility in organic solvents, and blue fluorescence in solution; and a minute quantity of what may be a lactam. The second, however, gave a small quantity of a product identical with the lactam obtained from the Beckmann transformation. The lactam must therefore have the structure (II), and this was confirmed by its oxidation with alkaline permanganate to phthalic acid in almost quantitative yield: no naphthalic acid could be detected. From the structure of the lactam (II) it follows that the oxime is (I).

Under drastic conditions *meso*benzanthrone formed a 2 : 4-dinitrophenylhydrazone in poor yield.

Attempts were made to see if the carbonyl group of *meso*benzanthrone is reduced to the CH·OH group by aluminium *iso*propoxide. Reduction was readily effected, but surprisingly resulted in the complete removal of oxygen to give a good yield of *meso*benzanthrene. A good method is thereby provided for the preparation of *meso*benzanthrene and certain substituted *meso*benzanthrenes. The method was successfully applied to the preparation of 3-chloro- and 3-bromo-*meso*benzanthrene, but 11-amino*meso*benzanthrone gave only unchanged material, probably owing to its insolubility in *iso*propanol; and 4-benzyl*meso*benzanthrone gave a small yield of what seemed to be the carbinol. So far as we are aware the one other example of the reduction of a carbonyl to a methylene group by the Meerwein–Ponndorf reagent is the slow conversion of 9 : 9-dimethylanthrone into the dihydroanthracene (Adkins and Rossow, "Organic Reactions," Vol. II, p. 191). The only other comparable reaction which comes to mind is the reduction of xanthone to xanthen by sodium and ethanol (Heller and von Kostanecki, *Ber.*, 1908, **41**, 1324; Kruber and Lauenstein, *ibid.*, 1941, **74**, 1693). We have reduced anthrone by aluminium *iso*propoxide and found that it gives anthracene. Presumably 9 : 10-dihydroanthranol is first formed and loses water to give anthracene (cf. Houben, "Das Anthracen und die Anthrachinone," p. 167, G. Thieme, Verlag, Leipzig).

The basic properties of the carbonyl group in *meso*benzanthrone are reflected in the formation of oxonium salts. Perkin (*J.*, 1920, 696), from the colour of the solution, surmised that *meso*benzanthrone forms an oxonium salt with concentrated sulphuric acid. By the Kofler method (Kofler and Kofler, "Mikromethoden zur Kennzeichnung organischen Stoffe und Stoffgemische," Universitätsverlag, Innsbruck, 1948) we have shown that an oxonium salt, m. p. 184°, is indeed formed. Trichloroacetic acid also gives an oxonium salt, but the weaker chloroacetic, benzoic, and adipic acids give only eutectic mixtures. Fluorenone and phenanthraquinone likewise form oxonium salts with trichloroacetic acid, that of the former compound having m. p. 37° which differs from the 58° assigned by Meyer (*Ber.*, 1910, **43**, 162). We repeated the preparation by Meyer's method and obtained yellow plates, m. p. 37°, thereby confirming the m. p. obtained by the micro-method. The pronounced tendency of *meso*benzanthrone and fluorenone to form oxonium salts is emphasised by the failure of benzylideneacetophenone to form an oxonium salt with trichloroacetic acid, in spite of the known fact that αβ-unsaturated ketones are particularly prone to oxonium compound formation (see, *e.g.*, Wheland, "Advanced Organic Chemistry," p. 41).

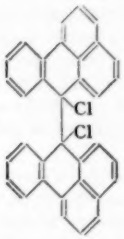
*meso*Benzanthrone and fluorenone form molecular compounds with picric acid and 1 : 3 : 5-trinitrobenzene. The isolation of these compounds is not easy, but their formation is conclusively shown by the Kofler "contact process."

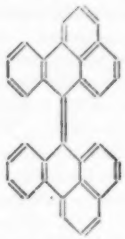
We subjected *meso*benzanthrone to the action of hydrazoic acid under a variety of conditions, but obtained only unchanged ketone.

*meso*Benzanthrone when heated with phosphorus pentachloride and oxychloride gave two products, both of which dissolve in benzene, ethanol, etc., to give yellow solutions with a vivid green fluorescence. One of these substances was obtained as orange needles, m. p. 390°, and contained chlorine. The mode of formation, analytical results, and

molecular weight of approximately 500 suggest that this substance is 7 : 7′-dichloro-7 : 7′-di*meso*benzanthrenyl (V). Treatment of *meso*benzanthrone with phosphorus oxychloride alone yielded a product which crystallised in yellow needles, m. p. 346—347°, which proved to be identical with the hydrocarbon obtained as one of the products when

(V)





(VI)

*meso*benzanthrone is distilled over zinc dust (Zinke *et al.*, *Monatsh.*, 1950, **81**, 878, 1137). We are indebted to Professor A. Zinke, of the University of Graz, for supplying us with a specimen. Our analytical figures indicate that the hydrocarbon is 7 : 7′-di*meso*benzanthrylidene (VI) which differs from the structure tentatively suggested by Zinke *et al.* (*loc. cit.*). Further work however is required before a structure can be assigned with finality.

Experimental

All chromatographic separations were effected on alumina (B.D.H. chromatographic), and the thermal behaviour of substances was examined on the Kofler hot-stage microscope (*Mikrochem.*, 1934, **15**, 242).

meso*Benzanthrone Oxime.*—Purified *meso*benzanthrone (10 g.), hydroxylamine hydrochloride (50 g.), and pyridine (250 ml.) were gently boiled for 70 hours. Most of the pyridine was then distilled off and the residue poured into water (150 ml.). Extraction with ether, followed by evaporation of the ethereal layer to a small volume and addition of the same volume of ethanol, gave a 85—95% yield of crude oxime, m. p. 160—165°. The oxime in benzene was passed down a column (18 × 1″) and on development with benzene *meso*benzanthrone passed rapidly through leaving the oxime at the top of the column as a dull yellow zone with a faint yellow fluorescence. Extraction of this zone with ethanol gave meso*benzanthrone oxime*, pale yellow rhombohedral plates (from methanol), m. p. 171° (6·8 g., 65%) (Found : C, 82·8; H, 4·5; N, 5·5. $C_{17}H_{11}ON$ requires C, 83·3; H, 4·5; N, 5·7%). The oxime is readily hydrolysed to *meso*benzanthrone by boiling ethanolic sulphuric acid, and even crystallisation from glacial acetic acid causes partial hydrolysis.

3-*Chloro*meso*benzanthrone oxime* (35%) was similarly prepared, and separated from methanol in pale orange prisms, m. p. 205° (Found : N, 5·2; Cl, 13·3. $C_{17}H_{10}ONCl$ requires N, 5·0; Cl, 12·7%).

Beckmann Rearrangement of meso*Benzanthrone Oxime.*—*meso*Benzanthrone oxime (3·0 g.), phosphorus pentachloride (3·8 g.), and phosphorus oxychloride (50 ml.) were gently boiled for 1½ hours, and the oxychloride removed by distillation. The residue was stirred with a little water and repeatedly extracted with benzene. The combined benzene extracts (600 ml.), when kept overnight, deposited a *chloro*-compound, which crystallised from ethanol in colourless needles, m. p. 288° (0·17 g.) (Found : N, 4·9; Cl, 13·1. $C_{17}H_{10}NCl$ requires N, 5·3; Cl, 13·4%). The filtrate was passed down a column (12 × 1″), and development with benzene gave a yellow zone of *meso*benzanthrone (0·24 g.) which quickly passed down the column. Continued development gave at the bottom a buff-coloured zone which on extraction with ethanol afforded the *lactam* (II), m. p. 234°, of 8-*o*-carboxyphenyl-1-naphthylamine (Found : C, 82·9; H, 4·6; N, 5·7. $C_{17}H_{11}ON$ requires C, 83·3; H, 4·5; N, 5·7%).

Structure of the Lactam (II).—The lactam (0·5 g.) in concentrated sulphuric acid (4 ml.) was added with stirring to water (50 ml.). The suspension was made alkaline with 6N-sodium hydroxide, and water was added to make the volume up to 125 ml. Potassium permanganate (3 g.) was added and the mixture refluxed for 17 hours. The product was proved to be phthalic acid by m. p. (205—210° on rapid heating), mixed m. p., fluorescein test, and preparation of the aniline salt, m. p. 154°. The complete absence of naphthalic acid was shown by the failure of the product to give a colour with concentrated sulphuric acid.

8-Bromo-1-naphthoic acid (12 g.) was converted by sodium azide (5 g.) and concentrated sulphuric acid (100 ml.) into 8-bromo-1-naphthylamine (10·6 g.), m. p. 82—86°, which with *o*-bromobenzoyl chloride afforded 8-*bromo*-*o*-N-*o*-*bromobenzoyl*-1-*naphthylamine*, elongated prisms (from methanol), m. p. 142° (Found: N, 3·3; Br, 38·9. $C_{17}H_{11}ONBr_2$ requires N, 3·5; Br, 39·5%). This substance (1·8 g.) and copper bronze (1·6 g.) were heated at 250—260° for 2 hours. The mixture was extracted with acetone and on evaporation gave a residue which was dissolved in benzene and chromatographed. Development with benzene gave a number of zones one of which occupied the same place on the column as that from the Ullmann product described below which yielded high-melting material. Extraction of this band with ethanol yielded 10 mg. of a substance, m. p. 224—230°, which when mixed with the Beckmann rearrangement product (m. p. 234°) melted at 226—228°. Both substances dissolved in sulphuric acid to give yellow solutions with a faint yellow fluorescence.

Ring-closure of 8-*Bromo*-1-*naphthoic Acid* o-*Bromoanilide.*—The acid chloride from 8-bromo-1-naphthoic acid (5 g.) and *o*-bromoaniline (8 g.) in benzene gave the *o-bromoanilide*, needles (from aqueous methanol), m. p. 145—146° (7·2 g.) (Found: N, 3·4; Br, 39·5. $C_{17}H_{11}ONBr_2$ requires N, 3·5; Br, 39·5%). The bromoanilide (2·0 g.) and copper bronze (1·8 g.) were stirred at 255—260° for 2 hours and worked up as above. Development of the column with benzene gave a zone with a strong blue fluorescence even in daylight. Elution of this zone and concentration of the eluate gave a *substance*, prisms [from light petroleum (b. p. 60—80°)], m. p. 102° (Found: C, 82·5; H, 4·6; N, 5·5. $C_{17}H_{11}ON$ requires C, 83·3; H, 4·5; N, 5·7%). On the column a large yellow zone with a yellow fluorescence remained which yielded *N*-phenylnaphthastyril, pale yellow needles (from light petroleum), m. p. 106° (Found: C, 83·1; H, 4·6; N, 5·7. Calc. for $C_{17}H_{11}ON$: C, 83·3; H, 4·5; N, 5·7%). There remained at the top of the column, directly below a black region of impurity, a fawn-coloured, non-fluorescent zone which was separated and extracted with methanol. Concentration of the extract gave a little material which, crystallised from methanol, had m. p. 240—250°. It contained no halogen and showed a big m. p. depression when admixed with the lactam (II). It is possible that this substance is the isomeric lactam.

Reduction of meso*Benzanthrone, etc.*—*meso*Benzanthrone (0·5 g.), *iso*propanol (20 ml.), and aluminium *iso*propoxide solution (10 ml.) (from 100 ml. of *iso*propanol and 5 g. of aluminium) were refluxed for 20 hours. The flask was then fitted with a Hahn condenser containing methanol, and slow distillation was carried out until all the acetone was removed and the volume was reduced to approx. 10 ml. A further quantity of *iso*propoxide solution (5 ml.) and *iso*propanol (20 ml.) was added and the solution boiled for 20 hours. The acetone was then distilled off and the solution concentrated to about 10 ml. The residue was treated with dilute sulphuric acid and extracted with boiling benzene. The extract was then chromatographed. Development with benzene gave a colourless zone showing strong violet fluorescence, which passed rapidly down the column to yield a colourless solid (0·37 g.), m. p. 75—77°, which crystallised from ethanol in almost colourless plates of *meso*benzanthrene, m. p. 80—82° (Found: C, 94·3; H, 5·3. Calc. for $C_{17}H_{12}$: C, 94·4; H, 5·6%). The product gave a picrate, red needles, m. p. 110—111° (lit., 110—111°), and dissolved in concentrated sulphuric acid with a faint red fluorescence.

Pure 3-chloro*meso*benzanthrone (1 g.), aluminium *iso*propoxide solution (15 ml.), and *iso*propanol (30 ml.) were gently boiled for 18 hours. Alternate distillation and refluxing were then carried out until no acetone was produced after 1 hour's refluxing. The product was worked up as above and chromatographed on a column (18″ × ¾″). Development with light petroleum–benzene (4 : 1) gave a blue fluorescent zone which passed quickly down the column and yielded 3-*chloro*meso*benzanthrene* (0·63 g.), rosettes (from light petroleum), m. p. 110° (Found: C, 81·2; H, 4·4; Cl, 13·8. $C_{17}H_{11}Cl$ requires C, 81·4; H, 4·4; Cl, 14·2%). 3-Bromo-*meso*benzanthrone similarly gave 3-*bromo*meso*benzanthrene* (70%), needles (from light petroleum), m. p. 116° (Found: C, 69·2; H, 3·7; Br, 26·4. $C_{17}H_{11}Br$ requires C, 69·1; H, 3·7; Br, 27·1%).

4-Benzyl*meso*benzanthrone (0·5 g.), aluminium *iso*propoxide solution (15 ml.), *iso*propanol (20 ml.), and benzene (100 ml.) were boiled for 25 hours; and then alternately distilled and refluxed for a further 5 hours. Working up the solution as above and chromatographing on a column (12 × 1″) gave a zone with a violet fluorescence typical of *meso*benzanthrenes, from which, however, only a trace of solid was obtained. A yellow zone which followed was washed through and deposited yellow prisms of what may be the 4-*benzyl*meso*benzanthrol* (20 mg.), m. p. 127—128° (Found: C, 90·8; H, 6·0. $C_{24}H_{18}O$ requires C, 89·5; H, 5·6%). An upper yellow layer on the column afforded unchanged benzyl*meso*benzanthrone (0·2 g.).

Anthrone (0·5 g.), aluminium *iso*propoxide solution (10 ml.), and *iso*propanol (20 ml.) were

boiled for 40 hours and then slowly distilled. A practically quantitative yield of anthracene was obtained.

Oxonium Salts of meso*Benzanthrones.*—The formation of oxonium salts was established by the microscopic technique of Kofler and Kofler (*op. cit.*). By this technique the melting-points of the components and of the molecular compound (*e.g.*, oxonium salts), and the eutectic points of the molecular compound and the two components are determined. The results are tabulated below.

Component A	Component B	M. p. of molecular compound (M)	Eutectic A–M	Eutectic B–M
*meso*Benzanthrone	Picric acid	142°	138°	115°
,,	Trinitrobenzene	140	138	116
,,	$CCl_3 \cdot CO_2H$	95	88	47
,,	H_2SO_4	184	140	—
Fluorenone	Picric acid	95	72	94
,,	Trinitrobenzene	80	72	75
,,	$CCl_3 \cdot CO_2H$	37	24	22
Phenanthraquinone	,,	138	133	39

The following pairs of substances formed only eutectics (m. p. in parentheses): *meso*benzanthrone–chloroacetic acid (53°), *meso*benzanthrone–adipic acid (148°), *meso*benzanthrone–benzoic acid (109°), benzylideneacetophenone–picric acid (49°), benzylideneacetophenone–trichloroacetic acid (53°).

Action of Phosphorus Pentachloride and Oxychloride on meso*Benzanthrone.*—*meso*Benzanthrone (0·5 g.) was boiled for 5 hours in phosphorus oxychloride (10 ml.) and phosphorus pentachloride (0·65 g.). The oxychloride was then distilled off, the residue triturated with water, and the resulting dark solid extracted with boiling benzene. Concentration of the extract, followed by chromatography on a column (8 × 1″), gave a yellow zone which moved rapidly down the column to give a yellow solution with a vivid green fluorescence. Concentration of this solution to about 10 ml. afforded orange needles of 7 : 7′-*dichloro*-7 : 7′-*di*meso*benzanthrenyl* (0·2 g.), m. p. 390° (Found: C, 81·8; H, 3·4; Cl, 14·1. $C_{34}H_{20}Cl_2$ requires C, 81·8; H, 4·0; Cl, 14·2%). From the column a red solid, m. p. 320°, was isolated but was not further investigated.

*meso*Benzanthrone (0·5 g.) and phosphorus oxychloride (10 ml.) were boiled for 1½ hours. The oxychloride was distilled off, and the residue triturated with water. Extraction of the residue with benzene (1—1½ l.) dissolved only a portion of the solid. The solution was concentrated to 100 ml. and then passed down a column (30″ × 1″). Development with benzene–light petroleum (b. p. 60—80°) (4 : 1) gave a greenish-yellow zone with a bluish-green fluorescence which was the first to be washed through. The solution, which exhibited a striking bluish-green fluorescence even in daylight, gave on concentration 7 : 7′-*di*meso*benzanthrylidene* (?), yellow needles (from benzene), m. p. 346—347° (Found: C, 95·0; H, 4·6. $C_{34}H_{20}$ requires C, 95·3; H, 4·7%).

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154. *The Infra-red Absorption of Pyrophosphates.*

By ERNST D. BERGMANN, U. Z. LITTAUER, and S. PINCHAS.

The infra-red spectra of inorganic and organic phosphates and pyrophosphates have been investigated. The origin of the observed absorption bands is discussed. The band at 930—950 cm.$^{-1}$ found in the spectra of the organic pyrophosphates is characteristic of the P–O–P bond.

DURING a study of organic pyrophosphates, it became desirable to investigate whether their infra-red spectra and those of inorganic salts of that acid exhibit a band characteristic of the P–O–P linkage. Whilst the infra-red absorption of the esters of several phosphorus oxyacids has been studied, *e.g.*, by Meyrick and Thompson (*J.*, 1950, 225) who assigned the main band in their spectrum to the P=O stretching frequency (1250—1260 cm.$^{-1}$) (cf. Colthup, *J. Opt. Soc. Amer.*, 1950, **40**, 397; Gore, *Discuss. Faraday Soc.*, 1950, No. 9, 138),

alkyl pyrophosphates do not seem to have been investigated.* Inorganic pyrophosphates have been studied by Laforgue-Kantzer (*Ann. Chim.*, 1950, **5**, 819); for the tetrasodium and disodium salts, *e.g.*, the following bands have been observed (cm.$^{-1}$):

$Na_4P_2O_7$	1666	1539	1449	1429	1250	1088	995	926	893	800
$Na_2H_2P_2O_7$ ...	—	1539	1449	1389	—	1076(s)	1030	943	893(s)	802(s)

In the present study, suspensions of silver orthophosphate, silver acetyl phosphate, and silver pyrophosphate in medicinal liquid paraffin were investigated and the following intense bands observed, respectively, in the 980—900-cm.$^{-1}$ region (see below): **947**, **914**, **903** cm.$^{-1}$. The last one very probably corresponds to the 893-cm.$^{-1}$ band reported for the sodium salts.

A number of alkyl phosphates and pyrophosphates was then compared in the 910—1060-cm.$^{-1}$ region of the typical covalent phosphate bands (Colthup, *loc. cit.*) (Table below).

Infra-red spectra of alkyl phosphates and pyrophosphates in the 910—1060-*cm.*$^{-1}$ *region.*
(*Solvent, carbon tetrachloride, cell thickness,* 0·1 *mm.*)

	Concn. (g./c.c. of solvent)	Bands in cm.$^{-1}$ (optical density)				
Phosphate.						
Methyl	0·022	—	1043 (1·60)	—	—	—
Ethyl	0·043	—	1036 (1·37)	—	974 (0·83)	—
n-Propyl	0·040	1051 (0·38) [a]	1039 (0·40)	998 (0·87)	—	—
*iso*Propyl ...	0·020	—	—	995 (2·0) [b]	—	931 (0·08) [c]
n-Butyl	0·017	—	1026 (0·81)	991 (0·39)	—	—
Pyrophosphate.						
Methyl	0·020	1046 (0·80)	—	970 (0·39)	—	—
Ethyl	0·048	1036 (1·55)	—	980 (1·15)	939 (1·20)	—
n-Propyl	—	—	—	—	—	—
*iso*Propyl ...	0·017	—	1006 (0·71) [b]	—	950 (0·45)	934 (0·27) [c]
n-Butyl	—	[1035(s)]	—	980	950 [d]	—

[a] Probably the propyl absorption. [b] Probably a superposition of the two bands expected. [c] Probably the *iso*propyl absorption. [d] Data of Daasch and Smith (*loc. cit.*).

In addition to the strong bands in that region, the substances show, of course, the intense above-mentioned P=O stretching frequency (*e.g.*: triethyl phosphate 1257 cm.$^{-1}$; tetraethyl pyrophosphate 1284 cm.$^{-1}$).

Colthup (*loc. cit.*) records for phosphate ions a band at 1100—1040 cm.$^{-1}$ only, but none corresponding to the intense 947-cm.$^{-1}$ peak, observed here for silver orthophosphate (Duval and Lecomte, *Bull. Soc. chim.*, 1947, 101, record a band at 970 cm.$^{-1}$; at least part of this discrepancy is probably due to the great breadth of the band and to the fact that the measurements have been made in a suspension, not in solution). The existence, in the spectra of phosphates, of two bands would seem probable from a comparison with the Raman frequences of the phosphate ion, which lie at 980 and 1082 cm.$^{-1}$ (Herzberg, "Infrared and Raman Spectra of Polyatomic Molecules," New York, 1945, p. 167). The 980-cm.$^{-1}$ frequency, however, is usually infra-red inactive, owing to symmetry conditions (being the ν_1 fundamental which is infra-red-inactive for a XY_4 molecule; Herzberg, *op. cit.*, p. 259). From the presence of the peak at 947 cm.$^{-1}$, one will conclude that this symmetry is destroyed in the silver salt. Pauling ("The Nature of the Chemical Bond," New York, 1940, p. 243) has also commented on the partly covalent character of the Ag–O bond and the distorted configuration of the phosphate ion in silver orthophosphate, as inferred from the bond-length measurements. The absence, in the inorganic phosphate, of the P=O stretching frequency (1240—1300 cm.$^{-1}$) of the covalent phosphates can be ascribed to hybridisation between the P=O and the P–O bonds.

The similarly situated two frequencies of the trialkyl phosphates recorded in the Table (at about 1030 and 980 cm.$^{-1}$, respectively) have very probably to be assigned to the $P(OR)_3$ grouping (Colthup, *loc. cit.*, records only one band in this region)—one to the

* After completion of this investigation, Daasch and Smith (*Analyt. Chem.*, 1951, **23**, 853) reported the spectra of methyl, ethyl, and *n*-butyl pyrophosphate. Their results agree fairly well with those recorded in the present paper.

stretching of all three alkoxy-groups in phase, the other to the stretching of two of them against the third. The same assignment appears likely for the analogous frequencies in the spectra of the alkyl pyrophosphates.

The validity of this assignment is supported by the following considerations: these two intense bands occur also with similar intensities—though occasionally shifted somewhat—in the spectra of the dialkyl phosphites and phosphonates (Meyrick and Thompson, *loc. cit.*) and in the substances studied by Gore (*loc. cit.*) which contain at least two alkoxy-groups linked to phosphorus. They are absent in substances such as $C_6H_5 \cdot PSCl_2$. Furthermore, no other vibration is likely to cause an absorption of such high extinction coefficient [*e.g.*, for triethyl phosphate, $\varepsilon_{1036} = 6 \times 10^2$, $\varepsilon_{974} = 4 \times 10^2$ (for 1 mole/l. and a cell of 1 cm. thickness)]. Thirdly, it is reasonable to expect that the stretching of the three P–OR bonds in phase will have a frequency similar to that of the symmetrical stretching in the phosphate ion which lies at 980 cm.$^{-1}$ (Herzberg, *op. cit.*, p. 167). This, incidentally, leads to the conclusion that the frequency of about 1030 cm.$^{-1}$ belongs to the unsymmetrical out-of-phase mode vibration of the three P–OR bonds (symmetrical vibration, lower in energy content). The assumption of Daasch and Smith (*loc. cit.*), that it corresponds to the PO–C bond, thus does not seem justified.

The Table shows that the pyrophosphate always contains one band more (970, 939, 950 cm.$^{-1}$) than the corresponding phosphate. This frequency must be characteristic of the P–O–P grouping and very probably represents its antisymmetrical stretching vibration (the symmetrical one would probably be very weak or even infra-red-inactive). It is not present as a distinct band in silver pyrophosphate (for the Raman spectrum of inorganic pyrophosphates, see Hanwick and Hoffmann, *J. Chem. Physics*, 1951, **19**, 708), but seems to manifest iself in the shift of the second phosphate band from 947 cm.$^{-1}$ (silver phosphate) to 903 cm.$^{-1}$ (silver pyrophosphate), possibly because of the hybridisation of the P–O–P bonds under the influence of the ionic charges (cf. Kalckar, *Chem. Reviews*, 1941, **28**, 71; Hill and Morales, *J. Amer. Chem. Soc.*, 1951, **73**, 1656).

The introduction of a branched alkyl (*iso*propyl) group causes a shift to longer wavelengths in the frequency of the 1030-cm.$^{-1}$ band and brings about its merging with the band at about 980 cm.$^{-1}$. An analogous effect can be deduced for the 1030-cm.$^{-1}$ band from the data reported by Meyrick and Thompson (*loc. cit.*) for the alkyl phosphites and phosphonates.

Attention is drawn to the unexpected disappearance of one band in the spectra of the *methyl* esters of both phosphoric and pyrophosphoric acid. One frequently finds, however, that the lowest member of a homologous series differs somewhat from the higher ones. Also in the recorded Raman spectrum of trimethyl phosphate (Simon and Schulze, *Naturwiss.*, 1937, **25**, 669), the 980-cm.$^{-1}$ band is missing.

Materials and Apparatus.—Silver orthophosphate was prepared according to Lipmann and Tuttle (*J. Biol. Chem.*, 1944, **153**, 571); silver pyrophosphate by precipitation of an ice-cold aqueous solution of pyrophosphoric acid with a 25% silver nitrate solution, washing with ice-water, and drying *in vacuo* over phosphoric oxide. For the preparation of silver acetylphosphate, the instructions of Lipmann and Tuttle (*loc. cit.*) were followed. The esters had the following properties: Triethyl phosphate (Limpricht, *Annalen*, 1865, **134**, 347), b. p. 78—80°/4·5 mm., n_D^{20} 1·4056. Trimethyl phosphate (Evans, Davies, and Jones, *J.*, 1930, 1310), b. p. 93°/29 mm., n_D^{20} 1·3961. Tri-*n*-propyl phosphate (*idem*, *ibid.*), b. p. 95°/0·5 mm., n_D^{25} 1·4139. Tri*iso*propyl phosphate (*idem*, *ibid.*), b. p. 76°/3 mm., n_D^{20} 1·4057. Tri-*n*-butyl phosphate (*idem*, *ibid.*), b. p. 136°/5 mm., n_D^{25} 1·4220. Tetramethyl pyrophosphate (Toy, *J. Amer. Chem. Soc.*, 1949, **71**, 2268), b. p. 118°/0·5 mm., n_D^{25} 1·4120. Tetraethyl pyrophosphate (Toy, *ibid.*, 1948, **70**, 3882), b. p. 132—134°/0·8 mm., n_D^{20} 1·4189. Tetra*iso*propyl pyrophosphate (*idem*, *ibid.*), b. p. 120°/0·1 mm., n_D^{25} 1·4150.

The apparatus used was a Perkin–Elmer Model 12 C Infra-red Spectrometer, mounted with a rock-salt prism. The slit width used was approx. 0·3 mm., varying somewhat from measurement to measurement.

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155. *The Stereochemical Course of the Conversion of 2-Ureido-alcohols into Oxazolidines. Part I.*

By GÁBOR FODOR and KÁROLY KOCZKA.

N-Cyano- (I) and *N*-carbamyl- (II; R = H) -(±)-ephedrine are converted quantitatively by treatment with acid into (±)-2-imino-**3**: 4-dimethyl-5-phenyloxazolidine (IV) with *inversion* of configuration. *N*-Carbamyl-(±)-ψ-ephedrine on identical treatment gives (±)-**3**: 4-dimethyl-5-phenyloxazolid-2-one (VII) with *retention* of configuration.

The cyclisations of the two diastereoisomers are strongly stereospecific, differing both in their end-products and in their mechanisms. This supports the concept that ephedrine and ψ-ephedrine are not only of different configuration, but that different conformations are stable in each diastereoisomer.

With cyanogen bromide each diastereoisomer cyclises with retention of configuration, giving the two imino-oxazolidines (IV) and (VIII; R = H). An explanation of this stereochemical process is given.

IT is known (Fodor, *Proc. Chim. Acad. Sci. Hungar.*, 1951, in the press; cf. Fodor, Koczka, and Szekeres, *Hungarica Chim. Acta*, 1951, in the press) that *O*-benzoyl-*N*-methyl-(±)-ephedrine and cyanogen bromide give *O*-benzoyl-*N*-cyano-(±)-ephedrine (I). We now find that, whereas alkaline hydrolysis of (I) leads to ephedrine (III), hydrolysis with dilute acid gives, in high yield, 2-imino-3: 4-dimethyl-5-phenyloxazolidine (IV), the configuration of (IV) being proved by its alkaline hydrolysis yielding exclusively ψ-ephedrine (V). This inversion of configuration can clearly occur either before or after the splitting off of the benzoyl group from the urea (II; R = Bz), presumably formed by the addition of water to (I). In order to decide between these two alternatives, *N*-carbamyl-(±)-ephedrine (II; R = H), prepared from (±)-ephedrine (III) hydrochloride, was also treated with dilute acid; (IV) was again obtained. It therefore seems reasonable to assume that inversion of configuration was induced by a nucleophilic attack by the ureido-oxygen atom, *trans* placed with respect to the hydroxyl group.

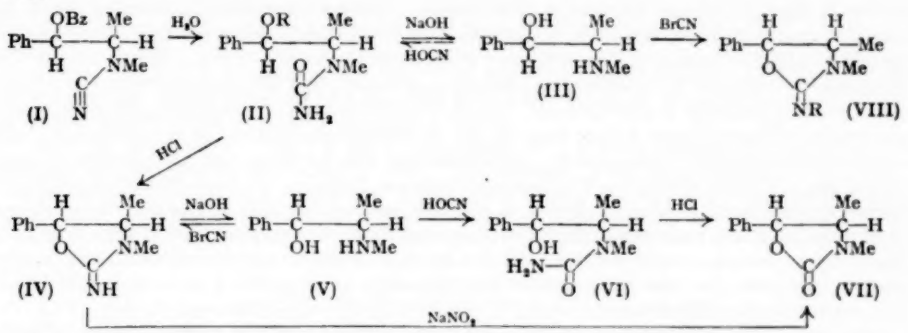
The preparation of substituted oxazoles by cyclisation of β-substituted alkyl-, *cyclo*-alkyl-, and aryl-ureas (which were sometimes too unstable for isolation) has frequently been reported (Stickings, *J.*, 1928, 3131; Pierron, *Ann. Chim.*, 1908, **15**, 191; Childs, Goldsworthy, Harding, Plant, and Weeks, *J.*, 1948, 2320; Gabriel, *Ber.*, 1917, **50**, 826; Takeda and Kuroda, *J. Pharm. Soc., Japan*, 1914, No. 449; 1921, No. 467; and Birckenbach and Linhard, *Ber.*, 1931, **64**, 1086), but apparently the stereochemical course of these cyclisation reactions has not been investigated.

As marked stereospecificity had already been noted among acylated diastereomeric 2-amino-alcohols, *e.g.* in N ⟶ O acyl migration reactions (Welsh, *J. Amer. Chem. Soc.*, 1947, **69**, 128; Fodor *et al.*, *J. Org. Chem.*, 1949, **14**, 340; *Nature*, 1949, **163**, 287; **164**, 917; 1951, **167**, 690) and in the thionyl chloride induced formation of the oxazole ring (Nagai and Kanao, *Annalen*, 1929, **470**, 157; Fodor *et al.*, *J. Org. Chem.*, 1949, **14**, 339), we have investigated the stereochemical course of the reaction of these diastereoisomeric 2-cyano-amino- and 2-ureido-alcohols with acid.

Close (*J. Org. Chem.*, 1950, **15**, 1131) has observed that fusion of (±)-ephedrine with urea furnishes a tetrahydroketoglyoxaline whereas from (+)-ψ-ephedrine an oxazolidone is obtained. This he regarded as evidence for the *cis*- and the *trans*-conformation of ψ-ephedrine and ephedrine, respectively, in agreement with our previous suggestions. It remains to be proved (Close, personal communication) whether the formation of the glyoxaline occurred with inversion or retention of configuration.

By treatment of (±)-ψ-ephedrine hydrochloride with potassium cyanate the urea (VI) was obtained. However, in conditions identical with those used for the conversion of (III) into (IV), (VI) gave (±)-3: 4-dimethyl-5-phenyloxazolid-2-one (VII) by loss of ammonia [Close obtained the (+)-form, m. p. 50—52°, by fusion of (+)-ψ-ephedrine with urea]. The oxazolidone (VII) must have been formed directly from (VI) and not *via* (IV),

as the latter was not affected by similar treatment. The configuration of (VII) is proved by its preparation from (±)-ψ-ephedrine and carbonyl chloride and from (IV) and nitrous acid.



The stereochemical course of the preparation of oxazolidones by treatment of amino-alcohols with carbonyl chloride (Stratton and Wilson, *J.*, 1932, 1132), urea (Close, Tiffany, and Spielman, *J. Amer. Chem. Soc.*, 1949, **71**, 1265), or alkyl carbonates (*inter al.*, Homeyer, U.S.P. 2 437 388) has not been examined previously, except in Close's recent work (*J. Org. Chem.*, 1950, **15**, 1131).

Our experiments show that the diastereoisomeric ephedrines react according to different mechanisms to furnish different products. Winstein and Boschan (*J. Amer. Chem. Soc.*, 1950, **72**, 4669) believe that cyclisation associated with inversion is caused by the rearward nucleophilic attack of the *trans*-placed neighbouring groups. In carbamyl-ephedrine the hydroxyl and the ureido-group must accordingly be *trans*-placed.

This stereochemical difference between ephedrine and ψ-ephedrine is greater than could be accounted for merely in terms of *configurational* differences, free rotation being assumed for identical conformations. Therefore, these experiments support our previous conclusions of a *conformational* difference between ephedrine and ψ-ephedrine (Fodor *et al.*, *loc. cit.*; Fodor, Kiss, and Sallay, *J.*, 1951, 1858).

The experimental observation that ephedrine and ψ-ephedrine can both form diastereo-isomeric oxazolidines with aldehydes (Welsh, *J. Assoc. Agr. Chem.*, 1948, **31**, 528) with retention of configuration seems apparently at variance with our suggestions. The reaction of ψ-ephedrine with cyanogen bromide under anhydrous conditions gave (IV), already obtained from (I) and from (±)-ephedrine *via* (II; R = H). Presumably cyanogen bromide reacted first with the hydroxyl group, and the derivative was then converted into the imino-oxazolidine of *trans*-conformation in respect of the phenyl and the *C*-methyl group. Under identical conditions ephedrine (III) furnished an isomeric product; this could be ephedrine cyanate or an imino-oxazolidine of *cis*-conformation in respect of the phenyl and the *C*-methyl group (*i.e.*, of ephedrine configuration). Hydrolysis of the benzoyl derivative of the product with dilute alkali gave benzamide and (±)-ephedrine. Consequently, the compound is the diastereoisomer (VIII; R = H) of the imino-oxazolidine (IV) obtained from ψ-ephedrine. Hence, like aldehydes, cyanogen bromide effected the formation of a cyclic compound from ephedrine with change of conformation but without inversion of configuration; while the diastereoisomer is formed from ψ-ephedrine without any stereochemical change. It is noteworthy that in the ephedrine series the process occurred in neutral or alkaline solution; in our conception of the Walden inversion, the splitting off of a hydroxyl anion must be assumed in all inversion reactions (Olson, *J. Chem. Phys.*, 1933, **1**, 418; Meer and Polanyi, *Z. physikal. Chem.*, 1932, *B*, **19**, 164), and this is undoubtedly facilitated by the presence of protons, either as hydroxyl-ion acceptors or as an electrophilic reagent (Welsh, *J. Amer. Chem. Soc.*, 1949, **71**, 3500). It is, therefore, hardly conceivable that (II; R = H), assumed to be an intermediate in the urea-fusion reaction (Close, *loc. cit.*), could cyclise in the presence of an excess of urea, with *inversion* of configuration.

From these experimental results it can be concluded that inversion does not occur during the cyclisation of ψ-ephedrine derivatives, in either acid or alkaline medium. This is because the rate of interaction of the functional groups, which are spatially near to each other, is always greater than that of inversion; before an inversion reaction could be significant a shift of the alcoholic hydroxyl group to a *trans*-position relative to the amino-group would be necessary. In acylated ephedrines, however, a nucleophilic attack by the *trans*-acylamino- or -ureido-group seems very likely, and it is evident that the rate of the inversion reaction is now greater. For retention of configuration, the groups in *trans*-conformation would have first to take up the *cis*-conformation, and the condensation could occur only thereafter; from energy considerations this procedure seems unlikely, as also is the possibility of inversion in alkaline or neutral medium, for then liberated hydroxyl anions cannot be neutralised. Hence in alkaline medium the rate of the inversion process is diminished to such an extent that the otherwise slow processes associated with retention of configuration can predominate. On the basis of different postulates, and assuming a *trans*-relationship for the phenyl and the *C*-methyl group, Welsh (*loc. cit.*) and Close (*loc. cit.*) reached similar conclusions.

The results of investigations of N ⟶ O acyl migrations in diastereoisomeric 2-acylaminocyclopentanols (Fodor and Kiss, *J.*, in the press) support this conclusion, as *trans*-2-acylaminocyclopentanols behave as do acylated ephedrines, whereas the behaviour of the *cis*-compounds compares with that of ψ-ephedrines.

Our original concept of the difference in the conformations of ephedrine and ψ-ephedrine seems therefore to be justified. Further investigations are necessary to establish whether the stereochemical course of the reaction of the ureido-derivatives is of general value in deciding the conformation and configuration of the diastereoisomeric 2-amino-alcohols.

Experimental

The assignments *trans* and *cis* are related in the amino-alcohols to the conformation of the functional groups, and in the oxazolidines to that of the phenyl and the *C*-methyl group.

O-Benzoyl-*N*-cyano-(±)-ephedrine (I) was prepared as described by Fodor, Koczka, and Szekeres (*loc. cit.*).

(±)-*Ephedrine from* O-*Benzoyl*-N-*cyano*-(±)-*ephedrine*.—A solution of sodium hydroxide (2·7 g.) in water (40 ml.) was added to one of *O*-benzoyl-*N*-cyano-(±)-ephedrine (10 g.) in methanol (40 ml.), and the mixture heated for 6 hours on the steam-bath. The alcohol was distilled off in a vacuum, the residue was shaken with benzene (4 × 50 ml.), the combined extracts were dried (Na_2SO_4), and the solvent was evaporated. The residue (5·4 g., 93·5%) was crystallised from light petroleum (70 ml.) and gave pure (±)-ephedrine (4·0 g.), m. p. 72—75° (Found: N, 8·6. Calc. for $C_{10}H_{15}ON$: N, 8·4%).

(±)-trans-2-*Imino*-3 : 4-*dimethyl*-5-*phenyloxazolidine* (IV) *Hydrochloride*.—*O*-Benzoyl-*N*-cyano-(±)-ephedrine (10 g.) was heated under reflux with 2N-hydrochloric acid (100 ml.) for 6 hours. Addition of excess of 2N-hydrochloric acid to the ice-cooled solution caused an oil to separate; this was extracted with ether (200 ml.). The residue, after removal of the solvent, was treated with ethanolic hydrogen chloride. Evaporation of the alcohol gave the *hydrochloride* (6·8 g., 88%), m. p. 232—234°; after recrystallisation from acetone–methanol (20 ml.) by addition of ether (20 ml.) this had m. p. 235° (Found: C, 59·4; H, 7·2; N, 12·5; Cl, 15·6. $C_{18}H_{19}ON_2Cl$ requires C, 58·5; H, 6·65; N, 12·35; Cl, 15·3%).

(±)-ψ-*Ephedrine from the Hydrochloride of* (IV).—The hydrochloride (5 g.) of (IV) was heated for 4 hours on the steam-bath with an aqueous solution (100 ml.) of sodium hydroxide (1·77 g.), with shaking, and the cooled solution then extracted portionwise with benzene (50 ml.). The solvent was removed from the dried extract leaving (±)-ψ-ephedrine (3·5 g., 85%), which, after crystallisation from ether, had m. p. 117—118°, not depressed on admixture with an authentic specimen.

With larger quantities of the hydrochloride, two mols. of aqueous sodium hydroxide were added to an aqueous solution of the hydrochloride followed by as much alcohol as was needed to effect solution. The solution was refluxed for 4 hours, the alcohol distilled off, and the product isolated as before.

N-*Carbamyl*-(±)-*ephedrine* (II; R = H).—Potassium cyanate (2 g., 0·025 mole) was added to (±)-ephedrine hydrochloride (5 g., 0·025 mole) in water (25 ml.), and the solution then refluxed for 2½ hours, during which a small amount of oil separated, and cooled in ice-salt. The

dried, white plates of the *urea* (3 g., 57·7%) were crystallised from ethyl acetate and then had m. p. 126—127° (Found: C, 63·4; H, 7·7; N, 13·4. $C_{11}H_{16}O_2N_2$ requires C, 63·5; H, 7·7; N, 13·5%).

N-Carbamyl-(±)-ψ-ephedrine (VI).—(±)-ψ-Ephedrine hydrochloride (5 g., 0·025 mole) in methanol (50 ml.) was added to a solution of potassium cyanate (2 g., 0·025 mole) in methanol (150 ml.), and the mixture heated under reflux for an hour. Potassium chloride was filtered off and the filtrate evaporated to dryness. The residue was crystallised from ethyl acetate (20 ml.), giving white plates of the *urea* (2·2 g.); after repeated recrystallisation this had m. p. 140—141° (Found: C, 63·25; H, 7·8; N, 13·2%).

Action of Hydrochloric Acid on the Diastereoisomeric Carbamyl Derivatives.—(±)-trans-2-*Imino*-3 : 4-*dimethyl*-5-*phenyloxazolidine* (IV) *hydrochloride from N-carbamyl-(±)-ephedrine.* A solution of *N*-carbamyl-(±)-ephedrine (1·56 g., 0·075 mole) in water (24 ml.) and 2N-hydrochloric acid (15 ml.) was refluxed for 3 hours; when the clear solution cooled the oxazolidine (IV) hydrochloride was obtained. This was purified by conversion into the base which was extracted with benzene. The solvent was removed from this, and the residue converted into the hydrochloride (1·9 g., 84%), m. p. 225—229°, of (IV), identical with that already obtained.

(±)-trans-3 : 4-*Dimethyl*-5-*phenyloxazolid*-2-*one* (VII) *from N-carbamyl-(±)-ψ-ephedrine.* A solution of *N*-carbamyl-(±)-ψ-ephedrine (1·56 g., 0·075 mole) in water (24 ml.), to which 5·13N-hydrochloric acid had been added, was refluxed for 3 hours, by which time the oil had crystallised. The solid (0·98 g., 66%) was dried and then crystallised from ether–light petroleum (1 : 1); the *oxazolidone* (VII) formed long white needles, m. p. 59—61° (Found: C, 69·1; H, 6·7; N, 7·3. $C_{11}H_{13}O_2N$ requires C, 69·1; H, 6·1; N, 7·3%). Close (*loc. cit.*) recorded m. p. 50—52° for the (+)-isomer. Ammonium chloride (0·04 g., 100%) was obtained from the mother-liquors.

(±)-trans-3 : 4-*Dimethyl*-5-*phenyloxazolid*-2-*one* (VII) *from* (±)-ψ-*ephedrine.* A benzene (5 ml.) solution of carbonyl chloride (0·8 g., 0·008 mole) was added to one of (±)-ψ-ephedrine (4 g., 0·024 mole) in benzene (50 ml.), which was then set aside for 12 hours. The precipitate (3·0 g., 64% based on ephedrine input) was shown by its m. p. to be ψ-ephedrine hydrochloride. The residue (1·5 g., 35% based on ephedrine input), obtained on evaporation of the filtrate, was crystallised from a mixture of ether (6 ml.) and light petroleum (6 ml.), and yielded long, white needles (1·2 g.), m. p. 57—61° not depressed on admixture of the sample with the oxazolidone (VII), obtained from *N*-carbamyl-ψ-ephedrine.

(±)-trans-3 : 4-*Dimethyl*-5-*phenyloxazolid*-2-*one* (VII) *from* trans-(±)-2-*imino*-3 : 4-*dimethyl*-5-*phenyloxazolidine* (IV) *hydrochloride.* Sodium nitrite (0·516 g., 0·075 mole) was added to a solution of the hydrochloride (1·69 g., 0·075 mole) of (IV) in water (9 ml.), and the solution was then boiled for ½ hour. When the solution cooled the separated yellow oil crystallised; the solid had m. p. 50—56°, mixed m. p. with authentic (VII) 57—61°. It was recrystallised from a mixture of ether (10 ml.) and light petroleum (10 ml.), and gave the oxazolidone (1·2 g., 84%), m. p. 59—61°.

(±)-*Tetrahydro*-2-*keto*-3 : 4-*dimethyl*-5-*phenylglyoxaline.*—Finely powdered *N*-carbamyl-(±)-ephedrine (3·12 g., 0·015 mole), urea (1·8 g., 0·03 mole), and ammonium chloride (0·8 g.) were heated to 170°, and the temperature kept at 170—175° for ½ hour, then raised to 200—210°, and kept at that value for a further 1 hour. The product, when cold, was washed portionwise with hydrochloric acid (5%; 60 ml.); the residue (1·8 g., 65%) had m. p. 140—145°, not depressed on admixture with Close's authentic compound obtained from (±)-ephedrine on urea fusion.

(±)-cis-2-*Imino*-3 : 4-*dimethyl*-5-*phenyloxazolidine* (VIII; R = H).—An ethereal (60 ml.) solution of cyanogen bromide (3·5 g., 0·033 mole) was added to one of (±)-ephedrine (11 g., 0·066 mole) in ether (200 ml.); ephedrine hydrobromide (8·1 g., 50% based on ephedrine input), m. p. 186—188°, was filtered off and the filtrate concentrated in a vacuum to 25 ml. Needles (1·5 g.), m. p. 71—73°, of the cis-*oxazolidine* separated and were crystallised from ether (Found: C, 68·8; H, 8·0; N, 14·2. $C_{11}H_{14}ON_2$ requires C, 69·4; H, 7·3; N, 14·7%). The filtrate was concentrated further and the residual oil treated with ethanolic hydrogen chloride. The product was crystallised from a mixture of chloroform (25 ml.), acetone (10 ml.), and ether (5 ml.), yielding the *hydrochloride* (4·2 g.), m. p. 215—217° (raised on further recrystallisation to 217°) (Found: C, 58·5; H, 6·6; N, 12·25; Cl, 15·6. $C_{11}H_{14}ON_2$,HCl requires C, 58·5; H, 6·8; N, 12·35; Cl, 15·3%).

(±)-cis-2-*Benzimido*-3 : 4-*dimethyl*-5-*phenyloxazolidine* (VIII; R = Bz).—(*a*) The crystalline base (VIII; R = H), obtained in the previous experiment from (±)-ephedrine (11 g.), was set aside at 0° with benzoyl chloride (0·89 g.) in pyridine (12 ml.) for 2 days. The mixture was then poured into water (100 ml.), the crystalline benzimido-compound (1·4 g.), m. p. 149—152°, being obtained.

(*b*) The crude base (3·6 g.) was benzoylated in pyridine (36 ml.) with benzoyl chloride (2·66 g.); the product (3·2 g.) had m. p. 148—151° and was identical with that from (*a*).

The combined products from (*a*) and (*b*) (4·6 g., 62%) were recrystallised from ethyl acetate; the *benzimido*-compound formed white plates, m. p. 151—153° (Found: C, 74·7; H, 6·8; N, 9·6. $C_{18}H_{18}O_2N_2$ requires C, 73·4; H, 6·1; N, 9·8%).

Hydrolysis of the Benzimido-oxazolidine (VIII; R = Bz).—A solution of sodium hydroxide (0·39 g., 0·01 mole) in water (20 ml.) was added to one of the benzimido-compound (1 g., 0·0033 mole) in alcohol (40 ml.). After the mixture had been refluxed for 3 hours, it was concentrated to 20 ml. and an equal volume of light petroleum added. The needles which separated were transformed during 24 hours into plates; these had m. p. 126—128°, undepressed on admixture with an authentic specimen of benzamide. The mother-liqueur gave a second crop of benzamide; the total yield was 73·2%. The most soluble product was (±)-ephedrine hydrochloride (0·15 g.), m. p. 184—186°.

trans-(±)-2-*Imino*-3 : 4-*Dimethyl*-5-*phenyloxazolidine* (IV) *Hydrochloride from* (±)-ψ-*Ephedrine*.—An ethereal solution (40 ml.) of cyanogen bromide (1·75 g., 0·0165 mole) was added to one of (±)-ψ-ephedrine (5·5 g., 0·033 mole) in ether (100 ml.) and benzene (80 ml.). In addition to ψ-ephedrine hydrochloride (3·9 g.), a hydrochloride (2·2 g.), m. p. 233°, was obtained when the oily product was treated with ethanolic hydrogen chloride. This gave no depression of melting point when mixed with an authentic specimen of (IV) hydrochloride.

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156. *The Relation between Configuration and Conjugation in Diphenyl Derivatives. Part I. The Enantiomorphism and Ultra-violet Absorption Spectra of Some 2 : 2′-Bridged Compounds.*

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Various methods which have been used to investigate the configuration of the diphenyl skeleton, as it is present in a large variety of compounds, are reviewed. Compounds have been prepared in which the diphenyl skeleton is forced to assume a non-coplanar configuration by joining of the 2 : 2′-positions to produce a strainless multiplanar bridge. The ultra-violet absorption spectra of these compounds indicate that conjugation between the two benzene rings of the diphenyl skeleton still occurs. The introduction of methoxyl groups into the 6 : 6′-positions of the diphenyl part of these molecules, which can have little steric effect on the already twisted molecules, reduces the conjugation but results in considerable long-wave absorption. This is attributed to interaction between the methoxyl groups and the benzene rings to which they are attached, with consequent reduction in the double-bond character of the 1 : 1′-bond between the benzene rings. 2 : 7-Dihydro-4′ : 1″-dimethoxy-3 : 4-5 : 6-dibenzazepinium-1-*spiro*-1‴-piperidinium iodide has been resolved through the camphorsulphonates and is highly optically stable.

FOR a number of years after the acceptance of the collinear structure for diphenyls the problem of their configuration attracted little attention. When suitable *o*-substituents are present, the two benzene rings cannot become coplanar or rotate freely about the 1 : 1′-bond. This can be demonstrated unequivocally by optical resolution of typical compounds. In intermediate cases, the compounds can be optically activated but cannot be resolved. In compounds without 2-substituents and in compounds with small 2-substituents, coplanarity is not prohibited (these compounds cannot even be activated) and it was at one time considered that the stabilising effect of resonance between the two rings

would operate to produce a structure in which at least the *preferred* configuration was a coplanar one. This view was supported by the results of *X*-ray crystal analysis of diphenyl (Dhar, *Indian J. Physics*, 1932, **7**, 43), which showed the molecule in the crystal to be coplanar and the 1 : 1′-bond distance to be 1·48 Å, and by calculation of the resonance energy of diphenyl from the heat of combustion, which gave a value of about 9 kcal./g.-mol. in excess of the sum of the resonance energies of the two benzene rings (Pauling and Sherman, *J. Chem. Physics*, 1933, **1**, 606, 679). The significance of the latter result is clearly diminished by the fact that diphenylmethane has been stated (Wheland, " The Theory of Resonance," 1944, p. 69) to have a comparable additional resonance energy.

During recent years, however, much rather conflicting evidence relating to diphenyl compounds has accumulated, some of which appears to indicate that even in diphenyl itself the preferred configuration of the isolated molecule is not coplanar. At the same time, a number of workers have suggested that partial loss of coplanarity is not necessarily associated with complete loss of resonance. Related to this concept is the growing body of evidence that substituents in the benzene ring may be forced out of the plane of the ring by other groups present (Klevens and Platt, *J. Amer. Chem. Soc.*, 1949, **71**, 1714; Bastiansen and Hassel, *Acta Chem. Scand.*, 1947, **1**, 489; Everard and Sutton, *J.*, 1949, 2312; 1951, **16**; Newman and Hussey, *J. Amer. Chem. Soc.*, 1947, **69**, 3023; Newman and Wheatley, *J. Amer. Chem. Soc.*, 1948, **70**, 1913; Bell and Waring, *J.*, 1949, 2689; Badger and Pearce, *J.*, 1950, 3072).

The configuration of the diphenyl skeleton, as it is present in a large variety of compounds, has been investigated by the following methods: (1) The optical resolution (or asymmetric transformation) of compounds containing substituents in one or more of the 2 : 2′ : 6 : 6′-positions, together with a consideration of relative optical stabilities. (2) *X*-Ray crystal analysis. (3) Electron-diffraction in the vapour phase. (4) Dipole-moment measurements. (5) Ultra-violet absorption spectra.

With regard to method (1) it must be emphasised that in the case of compounds of high optical stability we are dealing with the impossibility of achieving certain configurations rather than with the problem of preferred configurations; activation energies for the configurational changes involved in racemisation are of the order of 20—30 kcal./g.-mol. It has proved satisfactory to represent such compounds by models in which covalent interatomic radii provide the dimensional data.

While methods (2) and (3) give unambiguous information about the configuration of the molecule in *particular physical states*, method (5) gives direct information only about conjugation between the two phenyl rings, although conclusions involving the relation between resonance and coplanarity of the phenyl rings have then been drawn.

In an attempt to determine the extent to which the ultra-violet absorption spectrum of a diphenyl compound is in fact a means of determining its configuration, we have investigated compounds in which structural features have been introduced into the molecule so that the configuration is fixed within comparatively small limits. Before describing this work we discuss the general applicability of the various methods and the results which have been obtained by their use. It may be noted that London (*J. Chem. Physics*, 1945, **13**, 396) computed the numerical values of the energy levels in diphenyl on the basis of a " flat-plane " structure for diphenyl, and regarded the good agreement between the theoretical electronic transitions and the observed ultra-violet absorption spectrum as favouring the coplanar model.

X-Ray crystallographic investigations give information as to the configuration of a molecule in the crystal. In addition to preferred molecular configurations we have to take into account intermolecular cohesive forces, and it is thus evident that the results of *X*-ray crystal analysis, while giving certain molecular dimensions with great accuracy, do not necessarily throw much light on the preferred configuration of the isolated molecule. Dhar's conclusions (*loc. cit.*) were based on determinations of the space group and the number of molecules per unit cell in the crystal of diphenyl, which show that the molecule has a centre of symmetry and therefore that the two benzene rings are here coplanar (see also Hengstenberg and Mark, *Z. Krist.*, 1929, **70**, 283; Clark and Pickett, *J. Amer. Chem. Soc.*, 1931, **53**, 167; Dhar, *loc. cit.*; *Proc. Nat. Inst. Sci. India*, 1949, **15**, 11). Similarly,

Toussaint (*Acta Cryst.*, 1948, **1**, 43) concluded that 3 : 3′-dichlorobenzidine was planar (or nearly so) in the crystal, the chlorine atoms being in the "*trans*"-relationship. Yet in the crystal of 2 : 2′-dichlorobenzidine, Smare (*Acta Cryst.*, 1948, **1**, 150) found not only that the rings were at an angle of 72° to each other in a collinear arrangement having a 1 : 1′-bond of 1·53 Å, but further that the two chlorine atoms were "*cis*" rather than "*trans*," *i.e.*, were very much nearer together than one would have expected by comparison with the known preferred "*trans*"-configuration of ethylene dichloride in the vapour. Similarly, Fowweather and Hargreaves (*Acta Cryst.*, 1950, **3**, 81) concluded that in crystalline 2 : 2′-dimethylbenzidine dihydrochloride the respective dimensions were 71° and 1·52 Å, the two methyl groups having a "*cis*"-disposition. It is thus clear that some intramolecular repulsive forces may be overcome by the overriding effect of the cohesive forces in the forming crystal unit (cf. Bastiansen, *Acta Chem. Scand.*, 1949, **3**, 408).

Electron-diffraction investigation of vapours has the advantage of giving data concerning the *isolated* molecule and not a molecule which may have had to accommodate itself to the energetics of the crystalline state. Karle and Brockway (*J. Amer. Chem. Soc.*, 1944, **66**, 1974) favoured a non-coplanar diphenyl model with a 1 : 1′-bond of 1·54 ± 0·03 Å. Bastiansen (*loc. cit.*) added the refinement that in the collinear molecule the rings are inclined at an angle of 45° ± 10°. The same author deduced angles of 52° ± 10° and 54° ± 5° for 3 : 3′-dichlorobenzidine and 3 : 3′-dibromodiphenyl, respectively. For 2 : 2′-dichloro-, 2 : 2′-dibromo-, and 2 : 2′-di-iodo-diphenyl, Bastiansen (*Acta Chem. Scand.*, 1950, **4**, 926) found the angles to be 74°, 75°, and 79° respectively (1 : 1′-bond, 1·50 ± 0·03 Å), the halogen atoms being, surprisingly, "*cis*" rather than "*trans*." All these figures relate to average configurations. Those for diphenyl itself fit in reasonably well with what one might expect in comparing, by means of models, the now generally accepted preferred configuration in ethane with that of diphenyl, assuming that the 1 : 1′-bond is essentially single. In both molecules repulsive forces between hydrogen atoms are from this point of view looked on as the controlling factor (compare Pauling, "The Nature of the Chemical Bond," 1942, p. 219) and in both cases one should speak not of "restricted" rotation [a term to which Mills and Elliott (*J.*, 1928, 1291) gave a precise meaning in connection with compounds having observable optical activity] but of something more indefinite, *e.g.* "hindered" rotation.

Dipole-moment measurements of diphenyl compounds can provide two distinct types of information. With 2 : 2′-disubstituted diphenyls it is possible to determine whether or not the molecule is predominantly planar (since, if it is, the dipole moment will either be zero for the "*trans*"-planar configuration or have a readily calculable value for the "*cis*"-planar one). In fact, such measurements indicate non-coplanar structures (Bretscher, *Helv. Physica Acta*, 1929, **2**, 257; Weissberger and Sängewald, *Z. physikal. Chem.*, 1933, *B*, **20**, 145; Hampson and Weissberger, *J. Amer. Chem. Soc.*, 1936, **58**, 2111; Le Fèvre and Vine, *J.*, 1938, 967; Lumbroso, *Bull. Soc. chim.*, 1949, **16**, D 387). On the other hand, dipole-moment measurements of 4 : 4′-disubstituted diphenyls (where the groups in the 4- and the 4′-position are different) can contribute information about resonance interaction between the substituents in the two rings and hence between the two rings themselves. The dipole moment of 4-amino-4′-nitrophenyl (Le Fèvre and Le Fèvre, *J.*, 1936, 1130) shows that such interaction occurs.

Pickett, Walter, and France (*J. Amer. Chem. Soc.*, 1936, **58**, 2296) studied the ultraviolet absorption spectra of diphenyl compounds in which the four *ortho*-positions were (*a*) substituted and (*b*) unsubstituted. In the former case the spectra were essentially those of the two corresponding benzene compounds, but in the latter case the spectra were very different and showed, as with diphenyl itself, a high-intensity band at *ca.* 2500 Å with a maximal molecular extinction coefficient of *ca.* 20 000 which arises as a result of resonance between the two aromatic nuclei, the 1 : 1′-bond acquiring some double-bond character. Such conjugation of the two phenyl groups operates by overlapping of the π orbitals of the 1 : 1′-carbon atoms, and has generally been assumed to require the coplanarity of the two phenyl groups (see Wheland, *op. cit.*, p. 92, etc., for review and references). Further spectroscopic evidence of conjugation between the two rings in non-*ortho*-substituted diphenyls has been given by Gillam and Hey (*J.*, 1939, 1170), Pestemer

and Mayer-Pitsch (*Monatsh.*, 1937, **70**, 104), Calvin (*J. Org. Chem.*, 1939, **4**, 256), O'Shaughnessy and Rodebush (*J. Amer. Chem. Soc.*, 1940, **62**, 2906), Williamson and Rodebush (*ibid.*, 1941, **63**, 3018), and others.

However, diphenyls in which only two of the four *ortho*-positions are substituted, *e.g.*, 2 : 2′-dimethyldiphenyl, also fail to exhibit the characteristic intense diphenyl band, indicating the absence of conjugation between the two phenyl rings (O'Shaughnessy and Rodebush, *loc. cit.*; Williamson and Rodebush, *loc. cit.*). The conclusion has been drawn that this phenomenon is associated with inability to assume a coplanar structure owing to interference between the 2-substituents and the 2′- and 6′-hydrogen atoms, especially as 2 : 2′-dihydroxydiphenyl (where the interfering effect of the hydroxyl groups is comparatively small) has a spectrum showing the characteristics both of a conjugated diphenyl and of phenol (Williamson and Rodebush, *loc. cit.*), and is presumably an intermediate case. On the other hand, such compounds do not exhibit optical activity, and presumably their passage through coplanarity does not involve a significant energy barrier.

Friedel, Orchin, and Reggel (*J. Amer. Chem. Soc.*, 1948, **70**, 199) report that 2-methyl-, 2-methoxy-, and 2-hydroxy-diphenyl all show hindered rotation effects in their ultraviolet absorption spectra. Reduction in conjugation as a result of steric interaction between the 2-substituents and the 2′- and 6′-hydrogen atoms was inferred by these authors from the reduced intensities and slight short-wave shifts of the *ca.* 2500-Å conjugation bands. The bands at *ca.* 2840 Å in 2-hydroxy- and 2-methoxy-diphenyl were considered to be "phenoxy"-bands, originating in the unconjugated phenyl groups containing the substituents. The high intensities of these bands ($\varepsilon_{max.}$ *ca.* 5000) must be due in part to overlapping by the long-wave sides of the more intense conjugation bands; in simple phenols and alkoxybenzenes their intensities are *ca.* 2000 (see Morton, "Practical Aspects of Absorption Spectrophotometry," Royal Inst. of Chemistry, 1938).

The criteria used by Friedel *et al.* are essentially those which have generally been applied to the interpretation of the spectra of diphenyls with hindered rotation, although not all authors have specifically assigned any long-wave absorption features to unconjugated phenyl groups acting as partial chromophores. In some compounds, *e.g.*, 2-methyldiphenyl (Friedel *et al.*, *loc. cit.*), the only indication of any absorption contribution of this type is a faint inflection on the long-wave side of the conjugation band, and such small effects have sometimes been ignored, attention being concentrated on alterations in the conjugation band only.

Rodebush and Feldman (*J. Amer. Chem. Soc.*, 1946, **68**, 896) conclude that the ultraviolet absorption spectrum of diphenyl is not incompatible with a non-coplanar model but add: "All that can be stated with certainty from the spectrographic studies is that in the unsubstituted diphenyls the configuration is near enough to coplanarity to allow a resonance energy amounting to several large calories." This conclusion is an indirect one in the sense that it is based on the assumption that the appearance of the high intensity band at *ca.* 2500 Å is dependent on conjugation between the two phenyl groups, for which their approximate coplanarity is regarded as a necessary condition.

In the coplanar configuration the *resonance* energy of the parent diphenyl system is presumably maximal, but with the introduction of a 2-substituent two new factors are introduced: (1) the space-requirements of the 2-group in relation to the 2′- and 6′-positions; (2) the electronic interaction of the 2-substituent with the ring to which it is attached. The second factor can clearly either support or oppose the fundamental diphenyl resonance, while the first effect must always be in opposition to it. Most workers have concentrated on the first factor, and it would appear that in many cases they have attained good correlation of experiment and inference. But since 2 : 2′-dimethyldiphenyl has very little diphenyl absorption (O'Shaughnessy and Rodebush, *loc. cit.*) and yet introduction of 4 : 4′-dinitro-groups restores almost the full diphenyl conjugation band (Sherwood and Calvin, *J. Amer. Chem. Soc.*, 1942, **64**, 1350; compare Pickett, Groth, Duckworth, and Cuncliffe, *ibid*, 1950, **72**, 44), it would appear that the interaction of a substituent with the aromatic ring to which it is attached can in some cases be more important in determining the type of absorption than the sterically-sensitive interaction of the two aromatic rings. In our present incomplete state of knowledge, caution is necessary in interpreting the effect

of substitution on the "configuration" of a diphenyl as indicated by its ultra-violet absorption spectrum.

In this connection attention must be drawn to a frequently quoted (cf. Bastiansen, 1949, *loc. cit.*; Clar, *Spectrochim. Acta*, 1950, **4**, 116; Hodgkin and Pitt, *Ann. Reports*, 1950, **47**, 459) note by Merkel and Wiegand (*Z. Naturforsch.*, 1948, **3**, *b*, 93), who suggested that compounds containing two coplanar linked (or linked and bridged) benzene rings give steep absorption bands with well-resolved fine-structure, and that non-coplanarity is associated with broad absorption bands showing no fine-structure. On the basis of these criteria the experimental data for diphenyl indicated it to be planar in the crystalline state, and non-coplanar not only in the vapour state but also in solution. Merkel and Wiegand's conclusions are, however, not free from ambiguity. It has frequently been shown (for review, see Jones, *J. Amer. Chem. Soc.*, 1945, **67**, 2131) that the introduction of methylene bridges into compounds containing linked aromatic rings, resulting in the formation of strained rigid structures, may be accompanied by a marked enhancement of fine-structure, *e.g.*, as in fluorene. In fused polycyclic aromatic compounds symmetry restrictions result in some of the low-intensity electronic transitions being forbidden, unless accompanied by simultaneous vibrational transitions. Conversely, the broad high-intensity conjugation bands of compounds containing linked benzene rings are permitted, and are active in absorption without the necessity for simultaneous vibrational transitions. Furthermore, fine-structure in the crystalline state must be to some extent influenced by intermolecular lattice forces, and in solution by interaction with solvent molecules (as indicated by low-temperature studies in rigid solvents). For these reasons it seems that Merkel and Wiegand's criteria are more likely to distinguish between compounds which approximate to the polycyclic aromatic type, being both rigid and coplanar, and compounds containing linked benzene rings in which coplanarity may be possible (and indeed facilitated by resonance stabilisation) but may be opposed by steric factors and bond-angle restrictions in strainless bridges. Thus in 2 : 2′ : 6 : 6′-tetrasubstituted diphenyls fine-structure is associated with the low-intensity absorption contributions of the unconjugated partial benzenoid chromophores, and is here an indication not of coplanarity but of its absence.

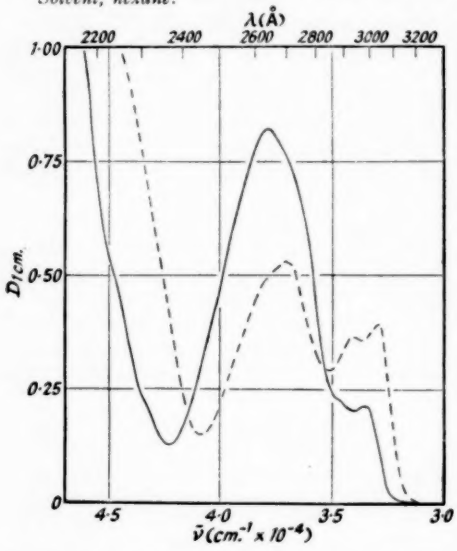


FIG. 1. —— 9 : 10-*Dihydrophenanthrene*, 4·59 × 10^{-5} *mole/l.* – – – 9 : 10-*Dihydro*-4 : 5-*dimethoxyphenanthrene* (I), 3·86 × 10^{-5} *mole/l. Solvent, hexane.*

By suitably joining the 2 : 2′-positions in diphenyl, molecules can be produced which combine the basic collinear diphenyl structure with a strainless multiplanar bridge and should therefore exist in optically stable enantiomeric forms, irrespective of further substitution in the 6 : 6′-positions. The simplest 2 : 2′-bridged diphenyl, fluorene, does not satisfy this requirement and is best regarded as a strained planar structure of the type noted above; it is thus unsuitable for our present purpose.

Bridging the 2 : 2′-positions in diphenyl by two methylene groups apparently involves no strain, the diphenyl skeleton remaining collinear and the carbon atoms of the two methylene groups having their normal tetrahedral angles. A model suggests that the angle between the two collinear phenyl rings in 9 : 10-dihydrophenanthrene is about 20° (compare Jones, *J. Amer. Chem. Soc.*, 1941, **63**, 1658). The ultra-violet absorption spectrum has been studied by several authors (Askew, *J.*, 1935, 509; Craig, Jacobs, and Lavin, *J. Biol. Chem.*, 1941, **139**, 277; Jones, *loc. cit.*; Braude, *J.*, 1949, 1902).

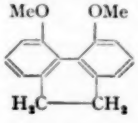
Our measurements are in agreement with the results of the above workers. The compound shows (Fig. 1 and table) a typical high-intensity diphenyl band at $\lambda_{max.}$ 2635 Å, $\varepsilon_{max.}$ 18 000, and a broad but definitely resolved low-intensity band at longer wave-length, $\lambda_{max.}$ 2995 Å, $\varepsilon_{max.}$ 4750. Jones (*loc. cit.*) ascribed this band to the bathochromic effect of the 9 : 10-methylene groups acting simply as alkyl substituents. This explanation was criticised by Braude (*loc. cit.*), who suggested that the relatively high intensity of the long-wave band was an indication of interaction between the two phenyl groups through the $\cdot CH_2 \cdot CH_2 \cdot$ linkage, so that this band had its origin in the same way as the long-wave band in fluorene ($\lambda_{max.}$ 3000 Å, $\varepsilon_{max.}$ 10 000), its lower intensity being attributed to a lower degree of interaction through two methylene groups. It seems more satisfactory to regard 9 : 10-dihydrophenanthrene as a diphenyl which is sufficiently non-coplanar for the conjugation through the 1 : 1′-bond * to be reduced, leading to the appearance of absorption contributions from the separate unconjugated phenyl chromophores.

Ultra-violet absorption spectra of 2 : 2′*-bridged diphenyls.*

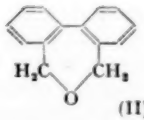
		Short-wave band				Long-wave band			
Compound	Solvent	$\lambda_{min.}$	$\varepsilon_{min.}$	$\lambda_{max.}$	$\varepsilon_{max.}$	$\lambda_{min.}$	$\varepsilon_{min.}$	$\lambda_{max.}$	$\varepsilon_{max.}$
Diphenyl	Hexane	2215	4 000	2475	19 000	—	—	—	—
	Ethanol	2220	5 100	2490	18 000	—	—	—	—
9 : 10-Dihydrophenanthrene	Hexane	2365	2 850	2635	18 000	—	—	2995	4 750
								(2895)	4 950
	Ethanol	2370	2 650	2640	17 000	—	—	2995	4 450
								(2895)	4 200
(I) 9 : 10-Dihydro-4 : 5-dimethoxyphenanthrene	Hexane	2450	3 800	2710	13 500	2850	7550	3045	10 500
				(2630)	12 500			2930	9 400
	Ethanol	2450	3 800	2720	13 500	2860	7350	3045	9 300
				(2630)	12 500			2930	8 650
(II) 2 : 7-Dihydro-3 : 4-5 : 6-dibenzoxepin	Hexane	2260	5 700	2500	16 500	—	—	—	—
(III) 2 : 7-Dihydro-4′ : 1″-dimethoxy-3 : 4-5 : 6-dibenzoxepin	Hexane	—	—	2530	8 650	2630	2450	2935	9 950
				(2460)	9 300			2835	9 400
(V) 2 : 7-Dihydro-3 : 4-5 : 6-dibenzazepinium-1-*spiro*-1‴-piperidinium bromide	Water	2240	4 500	2480	15 000	—	—	(2815)	2 250
								(2720)	4 750
(VIII) 2 : 7-Dihydro-4′ : 1″-dimethoxy-3 : 4-5 : 6-dibenzazepinium-1-*spiro*-1‴-piperidinium bromide	Water	2335	11 000	2375	11 500	2610	1450	2975	10 500

Wave-length values in parentheses denote inflections, as located by moving-plate spectrograms.

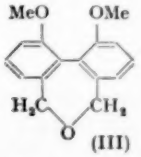
In 9 : 10-dihydro-4 : 5-dimethoxyphenanthrene (I) (Hall and Turner, *J.*, 1951, 3072) the conjugation band ($\lambda_{max.}$ 2710 Å) is of lower intensity than in 9 : 10-dihydrophenanthrene, but the long-wave band ($\lambda_{max.}$ 3045 Å) has increased in intensity and shows some fine-structure ($\lambda_{max.}$ 2930, 3045 Å) (Fig. 1).



(I)



(II)



(III)

Bridging of the 2 : 2′-positions of diphenyl by a 7-membered ring is particularly easy, corresponding to the formation of a strainless ring (compare Kenner and his co-workers, *J.*, 1911, **99**, 2101, and later papers). Thus 2 : 7-dihydro-3 : 4-5 : 6-dibenzoxepin (II) is

* Whenever the term 1 : 1′-bond is used the numbering refers to the diphenyl skeleton present in the molecule irrespective of the numbering of the molecule as a whole.

readily formed by the internal etherification of 2 : 2′-bishydroxymethyldiphenyl in presence of warm dilute mineral acid. The presence of methoxyl groups in the 6 : 6′-positions in the bishydroxymethyldiphenyl does not appear to diminish the ease of internal etherification and 2 : 7-dihydro-4′ : 1″-dimethoxy-3 : 4-5 : 6-dibenzoxepin (III) (Hall and Turner, *loc. cit.*) must also, in the light of this evidence, have a practically strainless structure. In this and the parent oxepin, the angle between the collinear phenyl rings is, according to the model, about 50°.

The ultra-violet absorption spectrum (Fig. 2) of the simple oxepin, however, shows no trace of any long-wave selective absorption, but only a high-intensity band at $\lambda_{max.}$ 2500 Å, $\varepsilon_{max.}$ 16 500 (hexane). Compared with diphenyl, the position of this band shows a slight long-wave shift (presumably owing to the bathochromic effects of the methylene groups) and a slight reduction in intensity of the maximum. The presence and intensity of this band, together with the absence of any long-wave absorption features (confirmed by moving-

FIG. 2.

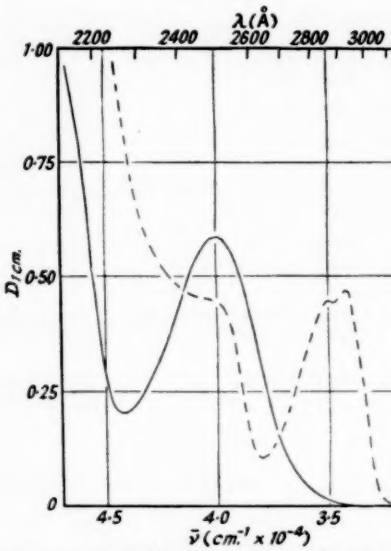


FIG. 3.

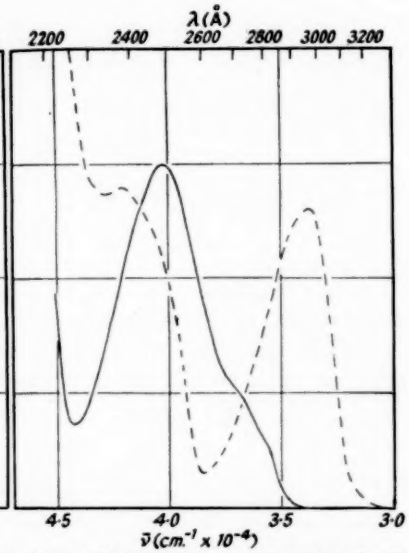


FIG. 2. —— 2 : 7-*Dihydro*-3 : 4-5 : 6-*dibenzoxepin* (II), 3·52 × 10^{-5} *mole/l.* – – – 2 : 7-*Dihydro*-4′ : 1″-*dimethoxy*-3 : 4-5 : 6-*dibenzoxepin* (III), 4·74 × 10^{-5} *mole/l. Solvent, hexane.*

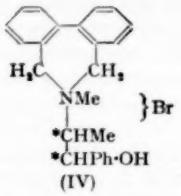
FIG. 3. —— 2 : 7-*Dihydro*-3 : 4-5 : 6-*dibenzazepinium*-1-spiro-1‴-*piperidinium bromide* (V), 5·05 × 10^{-5} *mole/l.* – – – 2 : 7-*Dihydro*-4′ : 1″-*dimethoxy*-3 : 4-5 : 6-*dibenzazepinium*-1-spiro-1‴-*piperidinium bromide* (VIII), 6·67 × 10^{-5} *mole/l. Solvent, water.*

plate spectrograms), would suggest that in the oxepin the phenyl groups are no less conjugated and hence no less coplanar than in diphenyl. Since, however, the oxepin cannot be coplanar, it follows that the diphenyl-type spectrum does not provide sure evidence for a coplanar configuration.

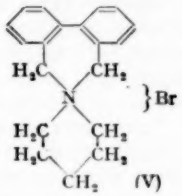
With the 4′ : 1″-dimethoxy-compound (III) the ultra-violet absorption spectrum (Fig. 2) shows a perceptible short-wave shift and marked reduction in intensity of the conjugation band, together with the appearance of a strong long-wave band at 2935 Å. Both these changes are indicative of marked reduction in conjugation between the phenyl rings, and on the basis of previous work would be interpreted as indicating a large departure from the presumed coplanarity of the parent oxepin. Such an interpretation is clearly untenable in view of the multiplanar configuration of the parent oxepin, and some other explanation of the differences in the spectra of the two oxepins, and also of the two dihydrophenanthrenes, must be sought.

Attention was now directed to the preparation of 7-ring-bridged diphenyls containing

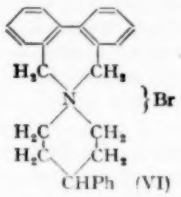
a group which would permit of attempted optical resolution. 2 : 2′-Bisbromomethyldiphenyl reacts vigorously with strong secondary bases to give dibenzazepinium compounds. Thus (+)-ephedrine gives 2 : 7-dihydro-1-(2-hydroxy-1-methyl-2-phenylethyl)-1-methyl-3 : 4-5 : 6-dibenzazepinium bromide (IV) which, if the cyclic system is dissymmetric, should be a mixture of diastereoisomerides. We were, however, unable to separate either the bromide or the corresponding iodide into two substances. Interaction of the dibromo-compound and piperidine gave 2 : 7-dihydro-3 : 4-5 : 6-dibenzazepinium-1-*spiro*-1‴-piperidinium bromide (V). Crystallisation of the corresponding (+)-camphorsulphonate and the (+)-α-bromocamphor-π-sulphonate from solvents did not lead to any conclusive separation into two fractions of different rotatory power. The crystallisations had none of the characteristics of second-order asymmetric transformation such as would have been possible and indeed expected had the configuration been unstable. In our view, the optical rotation of a compact rigid structure such as the one under investigation might well be expected to be of a low order, so that the *difference* in rotation between the two expected diastereoisomerides could easily be too small for the purposes of practical resolution.



(IV)



(V)

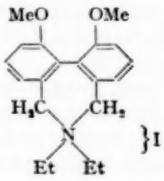


(VI)

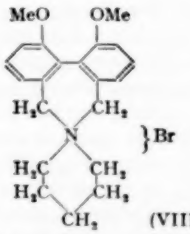
In the hope of augmenting the rotatory power, we prepared 2 : 7-dihydro-4‴-phenyl-3 : 4-5 : 6-dibenzazepinium-1-*spiro*-1‴-piperidinium bromide (VI) in which the CHPh group can only take part in the general dissymmetry because the diphenyl skeleton is twisted.

Crystallisation of the corresponding (+)-camphorsulphonate from various solvents led to no definite resolution, but on one occasion the (+)-α-bromocamphor-π-sulphonate when crystallised from water, gave two apparently different crops, one with $2H_2O$ and the other with $\frac{1}{2}H_2O$ of crystallisation. These salts, however, had practically indistinguishable rotations, and resolution clearly cannot be claimed.

As an alternative approach we condensed 2 : 2′-bisbromomethyl-6 : 6′-dimethoxydiphenyl with diethylamine and with piperidine, in the hope that introduction of the methoxyl groups, which could not have a determinative effect on the order of stability of the configuration of the quaternary salts as compared with that of the methoxyl-free compound, would enhance the rotation and thus make the resolution process practicable. It was noted that these quaternary salts were formed as readily as were those from the methoxyl-free dibromide, and it is evident that the formation of the 7-membered ring is less sterically affected than that of the 6-membered ring in the 9 : 10-dihydrophenanthrene series (Hall and Turner, *loc. cit.*).



(VII)



(VIII)

The quaternary (+)-camphorsulphonate derived from 1 : 1-diethyl-2 : 7-dihydro-4′ : 1″-dimethoxy-3 : 4-5 : 6-dibenzazepinium iodide (VII) proved difficult to manage as regards practical crystallisation, and the (+)-α-bromocamphor-π-sulphonate was obtained as, and remained, a gum. Of the quaternary salts derived from 2 : 7-dihydro-4′ : 1″-dimethoxy-3 : 4-5 : 6-dibenzazepinium-1-*spiro*-1‴-piperidinium bromide (VIII), the (+)-α-

bromocamphor-π-sulphonate, the hydrogen (+)-tartrate, and the (−)-menthyl phthalate could not be obtained crystalline. On the other hand, the (+)-camphorsulphonate crystallised well either from acetone or from acetonitrile. With the former solvent no evidence of resolution was obtained, but by an elaborate series of fractional crystallisations from acetonitrile a slight initial separation was ultimately developed and two salts having $[\alpha]_{5461}^{21}$ +19·0° and $[\alpha]_{5461}^{20}$ +24·7° (in ethanol) were isolated. To prepare the (−)-camphorsulphonate we used silver (−)-camphorsulphonate containing about 10% of (±)-salt and as a result the two extreme rotations found were $[\alpha]_{5461}^{18}$ −14·5° (*i.e.*, containing racemate) and $[\alpha]_{5461}^{19}$ −23·3°. Neither in the (+)- nor in the (−)-series was it possible to obtain the more soluble diastereoisomeride pure, but by treating the less soluble forms with potassium iodide we obtained iodides with $[\alpha]_{5461}^{22}$ −3·8° ± 0·2° [from the (+)-camphorsulphonate] and $[\alpha]_{5461}^{22}$ +4·0° ± 0·4° [from the (−)-camphorsulphonate] in acetonitrile. The completion of the purification of the active iodides was complicated by the appearance of dimorphic crystals (see Experimental).

The (+)-camphorsulphonate was not measurably racemised after being heated at 100° for two hours in ethanolic solution. The (+)-iodide was recovered with unchanged rotation after its aqueous solution had been boiled for 7 hours. When a solution of the (+)-iodide in a mixture of anisole and *cyclo*hexanol was boiled for 5 hours, the rotation of the recovered salt was unchanged. Partial racemisation of the (−)-iodide occurred when a *cyclo*hexanol solution was boiled (160°) for 8 hours, and complete racemisation when the process was continued for a further 8 hours. These facts are evidence of very considerable optical stability. The contrasting optical instability of 3 : 3′-diamino-2 : 2′ : 6 : 6′-tetramethoxydiphenyl (the dicamphorsulphonate of which mutarotates rapidly in solution at − 17°; Van Arendonk, Cupery, and Adams, *J. Amer. Chem. Soc.*, 1933, **55**, 4225) greatly strengthens our view that the methoxyl groups in (VIII) are only of secondary importance in affecting configurational stability.

The absorption spectrum (Fig. 3) of the 2 : 7-dihydro-3 : 4-5 : 6-dibenzazepinium-1-*spiro*-1‴-piperidinium cation (V) (examined as the bromide in water) shows a high-intensity band, $\varepsilon_{max.}$ 15 000, at a position $\lambda_{max.}$ 2480 Å, only slightly displaced to a shorter wave-length than that in diphenyl ($\lambda_{max.}$ 2490 Å, $\varepsilon_{max.}$ 18 000 in ethanol). This small shift and slight reduction in intensity suggest only a small departure from conjugation of the phenyl rings, of the same order as is indicated by the absorption spectrum for some 2-monosubstituted diphenyls. The sole evidence in the spectrum of (V) of any departure from diphenyl type is the existence of two long-wave inflections, $\lambda\lambda_{infl.}$ 2720, 2815 Å, which are just visible in the spectrogram as alterations in the contour of the long-wave foot of the high-intensity band; they can be located with precision by the moving-plate method. These inflections are of fairly low intensity, which is consistent with the high intensity of the short-wave band, on which in fact they are largely superimposed.

In (VIII) (Fig. 3) there is a large short-wave shift and appreciable reduction in intensity of the short-wave band, $\lambda_{max.}$ 2375 Å, $\varepsilon_{max.}$ 11 500 (in water, examined as the bromide), suggesting a considerably reduced interaction between the phenyl groups, as in the dimethoxyoxepin. Furthermore, as in the case of the dimethoxyoxepin (III), there is a well-resolved long-wave band of comparable intensity, $\lambda_{max.}$ 2975 Å, $\varepsilon_{max.}$ 10 500, which is completely separated from the 2375 Å band by a deep minimum at 2610 Å. In this compound, therefore, the short-wave band does not contribute significantly to the observed intensity of the long-wave absorption feature. There is a further striking departure from the normal diphenyl spectrum on the *short-wave* side of the 2375 Å band. Instead of the characteristic minimum which occurs at $\lambda_{min.}$ 2220 Å, $\varepsilon_{min.}$ 5100 for diphenyl itself, and at $\lambda_{min.}$ 2240 Å, $\varepsilon_{min.}$ 4500 in (V), in the dimethoxy-derivative (VIII) this minimum is almost abolished, relatively to the adjacent maximum, by the long-wave side of a very high-intensity band at still shorter wave-length with $\lambda_{max.}$ *ca.* 2100—2200 Å, $\varepsilon_{max.}$ *ca.* 40 000 or higher. It seems reasonable to identify this band as the high-intensity short-wave band of the benzenoid partial chromophore, but shifted to a longer wave-length. Its high intensity must be due in part to overlapping by the short-wave side of the displaced conjugation band at 2375 Å, but the relatively high intensity of the band at 2975 Å, which we shall regard as the long-wave band of the same chromophore, of the order of $\varepsilon_{max.}$ *ca.* 5000 per phenyl group, suggests

that there has been considerable enhancement of the intensities of both; the large red shift of the long-wave band is a further indication that the benzenoid partial chromophores are under the influence of strong bathochromic and hyperchromic factors.

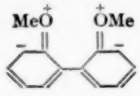
It is evident that the present results are not explicable solely on the basis of the hitherto accepted relationship between coplanarity and conjugation of the phenyl groups in substituted diphenyls. Thus the oxepins (II, III) and azepinium salts (V, VIII) would be expected to show no conjugation bands, as the two benzene rings in these compounds, although collinear, are not coplanar. Furthermore, the introduction of *oo'*-methoxyl groups, as in (III) and (VIII), should have no steric consequences if the phenyl groups are already incapable of conjugation in the parent compounds. The observed absorption spectra are in complete disagreement with both these expectations, but may be accounted for by the introduction of two hypotheses which have not been sufficiently considered in the interpretation of the absorption spectra of substituted diphenyls, though the necessity for them may also be seen from a scrutiny of some of the previous work in this field. These are (*a*) that coplanarity of the two benzene rings is not essential for the appearance of the conjugation band in *oo'*-substituted diphenyls, and large departures from coplanarity may be accommodated without complete loss of conjugation; and (*b*) that in diphenyls which show a conjugation band the introduction of additional groups may reduce the intensity of the band, even when their presence is without steric effect on the configuration. The justification for introducing the first hypothesis admittedly rests on the correct identification of the *ca.* 2400—2700 Å band in the present compounds as conjugation bands, and of the long-wave bands as those of the unconjugated partial chromophores of benzenoid character. As the groups which constitute the bridges between the phenyl groups in the present compounds are saturated, it is difficult to avoid the conclusion that any conjugation will indeed result in the formation of a diphenyl-type chromophore. Furthermore, notwithstanding the particular features which require interpretation, there is sufficient similarity between the spectra of the present compounds and those of both *o*-substituted and non-*o*-substituted diphenyls generally to provide support for extending both these familiar identifications to the spectra under discussion.

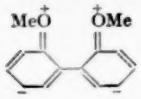
The relationship between the degree of conjugation in diphenyls and the angle between the planes of the phenyl groups is clearly a subject of considerable theoretical importance.* The literature dealing with the qualitative application of quantum-mechanical theory to unsaturated organic molecules is insistent that coplanarity is essential if resonance structures arising from conjugation are to make large contributions to the total structure, but it is difficult to find estimates of the extent to which conjugation occurs if coplanarity is prevented by steric effects. For the compounds examined in this work models suggest that in the oxepins and in the azepinium salts the angles between the ring planes are as large as 50°, thus permitting the introduction of the *oo'*-methoxyl groups without steric interactions occurring. In 9 : 10-dihydrophenanthrene, however, where the angle between the ring planes is *ca.* 20°, the *oo'*-methoxyl groups can only be introduced if some distortion of the molecule occurs. These deductions from models are borne out by the difficulty of bringing about ring closure of the dibromide to give 9 : 10-dihydro-4 : 5-dimethoxyphenanthrene, compared with the ease of formation of 9 : 10-dihydrophenanthrene itself. We should therefore expect the effect of the introduction of methoxyl groups on the spectrum of 9 : 10-dihydrophenanthrene to be different from that on the spectra of oxepin and azepinium compounds.

If hypothesis (*a*) is accepted for compounds (II) and (V), then we may say that the modifications in their spectra resulting from the presence of *oo'*-methoxyl groups are not primarily steric in origin but are due to the interaction of the methoxyl groups with their respective phenyl groups, leading to a decrease in conjugation across the 1 : 1'-bond. Resonance structures such as (IX) and (X) would be expected to reduce the double-bond character of this bond, and this effect would be additional to any steric effect that might

* [*Added in proof*, 18.1.52]. The authors are indebted to Dr. E. A. Braude for drawing their attention to a theoretical paper by Guy (*J. Chim. phys.*, 1949, **46**, 469) on the effects of steric hindrance by *oo'*-dimethyl groups, and of varying the angles between the ring planes, on the degree of conjugation and the ultra-violet absorption spectrum of diphenyl.

operate. In view of the well-known bathochromic and hyperchromic changes which follow the introduction of hydroxyl or alkoxyl into the benzene chromophore (cf. benzene with phenol and anisole; Morton, *op. cit.*), it is suggested that such structures are responsible

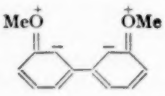
(IX) 

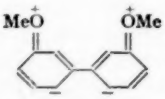
 (X)

for the decreased conjugation between the phenyl groups, as inferred from the relative intensities of the conjugation bands in (III) and (VIII), when compared with the parent oxepin and azepinium compounds.

In compound (I) distortion of the molecule resulting from the accommodation of the methoxyl groups may take the form of either an increased departure from coplanarity of the phenyl rings or out-of-plane bending of the methoxyl groups themselves. The former can only be achieved at the expense of the resonance energy associated with the conjugation of the phenyl groups and will also be opposed by the energy required to distort the valency angles of the dimethylene bridge (which is probably nearly strain-free for an angle of 20° between the ring planes). If our interpretation of the spectra of compounds (II) and (V) is correct it appears unlikely that such distortion would greatly affect the intensity of the conjugation band. But we should expect the methoxyl groups to exert what we may term their independent substituent effect on the benzene rings, as they do in compounds (III) and (VIII). If, however, the molecular distortion takes the form of bending of the methoxyl groups out of the planes of their respective phenyl rings, then their independent substituent effect on the phenyl rings (with its consequent reduction of the 1 : 1′-bond conjugation) will not operate in full; and the reduction in intensity of the conjugation band will be less than in the dimethoxy-oxepin and -azepinium cation. This, in fact, is what we have observed.

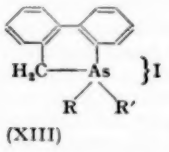
It is clear that the non-steric reduction of conjugation in diphenyls by methoxyl groups should be operative when these are introduced into positions where steric effects are completely absent. Thus, for *mm′*-dimethoxydiphenyl structures such as (XI) and (XII) will reduce the double-bond character of the 1 : 1′-link, and hence favour the unconjugated structure. This has, in fact, already been observed experimentally by Williamson and Rodebush (*loc. cit.*), who determined the absorption spectra of *oo′*-, *mm′*-, and *pp′*-dimethoxydiphenyl. The *oo′*-derivative shows no high-intensity band in the 2500—2700 Å region, but only a band at *ca.* 2800 Å, $\varepsilon_{max.}$ *ca.* 6000. The *pp′*-derivative gives a conjugation band of increased intensity and at longer wave-length, compared with diphenyl, owing to the favourable orientation of the auxochromic groups; furthermore, there are no long-wave absorption features. The *mm′*-derivative, however, gives a conjugation band of lower intensity than diphenyl, with only a small long-wave shift, and in addition shows a well-resolved band at *ca.* 2900 Å, of about the same intensity as in the *oo′*-compound. Williamson and Rodebush noted that these long-wave bands were similar to the band shown by anisole, and pointed out that in the *mm′*-derivative the methoxyl groups had no steric influence on the possible coplanarity of the molecule. Rather similar differences were noted in comparing the three corresponding dicarboxydiphenyls, though no long-wave absorption features were found in the spectrum of the *mm′*-isomer. It seems likely that many other substituents will be found to reduce the conjugation in diphenyls when introduced into the 3 : 3′-positions; results which have been obtained with various fluoro-derivatives will be given in a subsequent paper in this series.

(XI) 

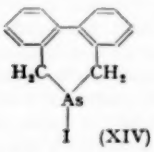
 (XII)

The absorption spectra of some arsenic compounds which have been examined by Mann and his co-workers may be briefly considered in the light of the suggestions made above. In compounds of type (XIII; R = Me, R′ = Me or Ph) absorption bands were found

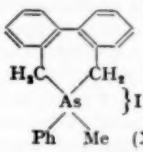
(Cookson and Mann, *J.*, 1949, 2888) at *ca.* 2700 Å, $\varepsilon_{max.}$ *ca.* 10 000, which were tentatively regarded as conjugation bands. As the angle between the planes of the bridged benzene



(XIII)



(XIV)



(XV)

rings in such compounds was estimated to be *ca.* 34°, the occurrence of a conjugation band of reduced intensity was ascribed to the ability of the benzene groups to oscillate through the coplanar configuration.

In compounds (XIV) and (XV) no such bands were observed, the absorption curves rising smoothly with decreasing wave-length in the 2400—3000-Å region and more steeply at shorter wave-lengths to very high values at *ca.* 2300 Å (Beeby, Mann, and Turner, *J.*, 1950, 1923). The absence of conjugation bands in the spectra of these 6-arsa-1 : 2-3 : 4-dibenzo*cyclo*hepta-1 : 3-diene derivatives was explained on the basis of rigid non-coplanar configurations with an estimated angle between the ring planes of *ca.* 63°.

It is sufficient to note here that the appearance of diphenyl-type conjugation bands in the dihydroarsanthridinium salts (XIII) is alternatively explicable on the basis of the suggestion made above that conjugation may still exist in non-coplanar diphenyls with 2 : 2′-bridges, without the necessity for assuming oscillation through the coplanar state of molecules which would be expected to be essentially rigid, as is indeed postulated for compounds of types (XIV) and (XV). The spectra of (XIII; R = Me, R′ = Me or Ph) also show marked inflections at *ca.* 2800 Å, which may be regarded as absorption contributions from the unconjugated benzene partial chromophores. The presence of these long-wave inflections tends to support the identification of the more intense bands at *ca.* 2700 Å as conjugation bands, as the spectra thus contain the complete system of bands to be expected in diphenyls of this type. The spectra of (XIV) and (XV), according to our hypothesis, would also be expected to show conjugation bands. These bands are absent, however, as are long-wave bands from the partial chromophores, which would be expected to be prominent in a completely unconjugated diphenyl.

For these reasons we consider that the spectra of (XIV) and (XV) are determined, not only by the possibility or otherwise of diphenyl-type conjugation, but by some other structural factors, which may be associated with the heterocyclic bridge, and we agree with Cookson and Mann that further investigation of the spectra of heterocyclic arsonium salts would be of interest.

We conclude that the ultra-violet absorption spectrum of a substituted diphenyl must be used with considerable reserve as a criterion of coplanarity or otherwise. The deductions drawn from earlier work in this field, based on comparisons between relatively simple *o*-, *m*-, and *p*-, or *oo*′-, *mm*′-, and *pp*′-substituted compounds, are probably reliable in the main, though some unexplained anomalies have been noted when the substituents were strong auxochromes, as in the case of the dimethoxy- and dicarboxy-diphenyls discussed above. For a particular diphenyl both the *position* and the *nature* of the substituent groups will determine the relative importance of steric and non-steric factors on the strength of conjugation, as indicated by the absorption spectrum.

Experimental

Spectroscopic Methods.—Absorption spectra were measured on a double-beam automatic-recording spectrophotometer designed and built by Holiday and Sutton (to be published). The records obtained are linear in optical density (*D*) against wave-number, as shown in Figs. 1—3, which are direct tracings from the original spectrograms after correction for small instrumental zero errors, obtained by checking the same test solutions at maxima and minima on a Unicam single-beam manual spectrophotometer. All compounds were also examined by

the moving-plate, logarithmic-cam method devised by Holiday (*J. Sci. Instr.*, 1937, **14**, 166) in order to locate more accurately any poorly-resolved fine-structure, especially in the weaker long-wave bands. These were more evident in hexane than in ethanol solution; water was used as solvent for the azepinium salts.

2 : 7-*Dihydro*-1-(2-*hydroxy*-1-*methyl*-2-*phenylethyl*)-1-*methyl*-3 : 4-5 : 6-*dibenzazepinium Bromide* (IV).—A solution of (−)-ephedrine hemihydrate (19·2 g., 2·2 mols.) in benzene (200 c.c.) was dried (Na_2SO_4). The filtered solution was warmed to *ca.* 50°, and 2 : 2′-bisbromomethyldiphenyl (17 g., 1 mol.) in benzene (90 c.c.) at 50° added to it. The mixture was kept for several hours with intermittent warming; a gum gradually separated. The solution was decanted, and the gum washed several times with benzene and then treated with water. The *bromide* eventually crystallised and was filtered off at 0° and recrystallised from methanol (13·7 g., 60%) (Found: Br, 17·4. $C_{24}H_{26}ONBr,CH_3{\cdot}OH$ requires Br, 17·5%); it had $[\alpha]_{5461}^{25}$ +53·5°, $[\alpha]_{5791}^{25}$ +44·0° (*c*, 1·000 in " AnalaR " chloroform). Fractional crystallisations from methanol produced no change in the specific rotation.

Treatment of a concentrated aqueous solution of the bromide with a saturated solution of potassium iodide gave the sparingly soluble *iodide*, which crystallised in the presence of ethanol in rectangular plates, sometimes coalescing into cubes, and beginning to decompose at 136° (Found: C, 60·3; H, 6·2; I, 24·4. $C_{24}H_{26}ONI,C_2H_5{\cdot}OH$ requires C, 60·35; H, 6·2; I, 24·5%); this had $[\alpha]_{5461}^{20}$ +38·2°, $[\alpha]_{5791}^{20}$ +30·7° (*c*, 1·205 in " AnalaR " chloroform). Fractional crystallisations from ethyl alcohol produced no significant changes in specific rotation.

The iodide later crystallised from acetone in an unsolvated form, having m. p. 226—228° (decomp.) and $[\alpha]_{5461}^{23}$ +41·4°, $[\alpha]_{5791}^{23}$ +33·5° (*c*, 1·2685 in " AnalaR " chloroform) (Found: I, 26·4. $C_{24}H_{26}ONI$ requires I, 26·9%). The specific rotation was unchanged after fractional crystallisation from (*a*) acetone and (*b*) water.

2 : 7-*Dihydro*-3 : 4-5 : 6-*dibenzazepinium*-1-spiro-1′′′-*piperidinium Bromide* (V).—A chloroform solution of piperidine (8·5 g., 2 mols.) was added gradually to a chloroform solution of 2 : 2′-bisbromomethyldiphenyl (17 g., 1 mol.) (Hall, Lesslie, and Turner, *J.*, 1950, 711); after the brisk reaction was over the mixture was warmed for 5 minutes and then treated with light petroleum (b. p. 40—60°). After decantation of the supernatant liquor the thick oily material formed was dissolved in methanol. Addition of ether precipitated the solid bromide, which was then crystallised from water, the *dihydrate* separating as prisms, m. p. 70—74° (yield, 72%) (Found: Br, 20·9. $C_{19}H_{22}NBr,2H_2O$ requires Br, 21·0%). The anhydrous bromide had m. p. 255°.

2 : 7-*Dihydro*-3 : 4-5 : 6-*dibenzazepinium*-1-spiro-1′′′-*piperidinium* (+)-*Camphorsulphonate*.—Aqueous ethanolic solutions of the above bromide (37·5 g.) and the equivalent silver (+)-camphorsulphonate were mixed, and the resulting suspension was boiled for ½ hour. Filtration, followed by evaporation to dryness, gave 49 g. of the *spiro*-camphorsulphonate. The product was systematically crystallised from absolute ethanol, but no separation into crops of different specific rotation was observed. Similar crystallisation of 42 g. of the camphorsulphonate from acetonitrile again effected no resolution. Crystallisation from anisole and from chloroform, in which the salt was very soluble, gave similar results. The pure salt had $[\alpha]_{5791}^{20}$ +11·1° ± 0·3°, $[\alpha]_{5461}^{20}$ +14·0° ± 0·3° (*c*, 1·5—5·0 in water) (Found: C, 70·6; H, 7·5. $C_{29}H_{37}O_4NS$ requires C, 70·3; H, 7·5%). The quaternary iodide prepared from the *camphorsulphonate* was inactive.

2 : 7-*Dihydro*-3 : 4-5 : 6-*dibenzazepinium*-1-spiro-1′′′-*piperidinium* (+)-α-*Bromocamphor*-π-*sulphonate*.—Interaction of the bromide (V) in ethanolic solution with one molecular proportion of silver (+)-α-bromocamphor-π-sulphonate, followed by filtration and evaporation, gave a crystalline *salt*, which was submitted to fractional crystallisation from (*a*) ethanol, (*b*) ethanol–ether, (*c*) benzene–light petroleum, and (*d*) acetonitrile. Over 70 crops were obtained having approximately the same rotation, namely, $[\alpha]_{5791}^{20}$ +50·7° ± 0·5°, $[\alpha]_{5461}^{20}$ +60·4° ± 0·5° (in water), and $[\alpha]_{5791}^{20}$ +56·4° ± 0·5°, $[\alpha]_{5461}^{20}$ +67·2° ± 0·5° (in chloroform) (Found: C, 60·8; H, 6·4. $C_{29}H_{36}O_4NBrS$ requires C, 60·6; H, 6·3%).

4-Phenylpyridine was prepared essentially by the method of Haworth, Hey, and Heilbron (*J.*, 1940, 349). From four experiments in each of which 60 g. of aniline were used, a total of 176 g. of mixed phenylpyridines, b. p. 140—142°/13 mm., was obtained. By successive freezings and crystallisations from light petroleum (b. p. 60—80°) 4-phenylpyridine (28 g.), m. p. *ca.* 60°, was obtained. A boiling alcoholic solution (3400 c.c.) containing picric acid (39·4 g.) and crude 4-phenylpyridine (26·65 g.) gave pure 4-phenylpyridine picrate, m. p. 196°, which was filtered off without the solutions being allowed to cool (the cooling mother-liquor deposited a mixture of 2-, 3-, and 4-isomerides). The original residues from which the 4-phenylpyridine had been obtained by freezing were caused to yield further quantities of 4-phenylpyridine picrate by

treating them in boiling ethanolic solution with a quarter of the theoretical amount of picric acid and filtering at the boiling point. A total of 43·5 g. of 4-phenylpyridine picrate was obtained and gave 17·5 g. of pure 4-phenylpyridine.

2 : 7-*Dihydro*-4‴-*phenyl*-3 : 4-5 : 6-*dibenzazepinium*-1-spiro-1‴-*piperidinium Bromide* (VI).—A benzene solution of 4-phenylpiperidine (19 g., 2 mols.; obtained by reducing 4-phenylpyridine with sodium and ethanol) was added to a benzene solution of 2 : 2′-bisbromomethyldiphenyl (19 g., 1 mol.). The mixture was gently warmed for 10 minutes after the brisk reaction was over. Light petroleum (b. p. 60—80°) was added. An oil separated which became solid on stirring and was crystallised thrice from water. 2 : 7-*Dihydro*-4‴-*phenyl*-3 : 4-5 : 6-*dibenzazepinium*-1-spiro-1‴-*piperidinium bromide* (15·5 g.) was obtained as stout prisms, m. p. (indef.) >300° (Found : C, 68·6; H, 7·0; Br, 18·45. $C_{25}H_{26}NBr,H_2O$ requires C, 68·5; H, 6·4; Br, 18·2%).

2 : 7-*Dihydro*-4‴-*phenyl*-3 : 4-5 : 6-*dibenzazepinium*-1-spiro-1‴-*piperidinium* (+)-*camphorsulphonate* was prepared in aqueous solution from 15·5 g. of the bromide (VI). Crystallisation from water, aqueous ethanol, ethanol, or acetonitrile was ineffective in achieving resolution. The salt from ethanol was solvated and had $[\alpha]_{5791}^{20}$ +18·2° ± 0·2°, $[\alpha]_{5461}^{20}$ +21·6° ± 0·2° (*c*, 2·5 in ethanol) (Found : C, 71·0; H, 7·4. $C_{35}H_{41}O_4NS,1\frac{1}{2}C_2H_5{\cdot}OH$ requires C, 71·2; H, 7·4%).

2 : 7 *Dihydro*-4‴-*phenyl*-3 : 4-5 : 6-*dibenzazepinium*-1-spiro-1‴-*piperidinium* (+)-α-*bromocamphor*-π-*sulphonate*, prepared in ethanc solution from 13 g. of the above bromide, could not be resolved by crystallisation from ethanol, acetone, or acetonitrile. Crystallisation from acetonitrile sometimes gave voluminous hair-like needles and sometimes stout plates into which the first form passed when kept in contact with solvent; this change occurred in a few seconds when a suspension of the needles was inoculated with the other form. Crystallisation from water also gave no definite indication of resolution although striking differences in crystalline form and solubility were observed. Different *hydrates* were obtained and all had the same specific rotation, $[\alpha]_{5791}^{20}$ +47·8° ± 0·3°, $[\alpha]_{5461}^{20}$ +57·0° ± 0·3° (in chloroform). Different crops were obtained which were either spherical aggregates of needles or sprigs of foliated crystals (Found : C, 61·6; H, 6·2. $C_{35}H_{40}O_4NBrS,2H_2O$ requires C, 61·2; H, 6·4%. Found : C, 63·5; H, 6·4. $C_{35}H_{40}O_4NBrS,\frac{1}{2}H_2O$ requires C, 63·7; H, 6·4%). Recrystallisation of the above hydrates gave *salts* having $\frac{1}{2}H_2O$ and $1\frac{1}{2}H_2O$ respectively (Found : C, 62·4; H, 6·4. $C_{35}H_{40}O_4NBrS,1\frac{1}{2}H_2O$ requires C, 62·0; H, 6·4%). Over 60 crops of (+)-bromocamphorsulphonate were examined. The quaternary picrate prepared from the bromocamphorsulphonate was inactive.

1 : 1-*Diethyl*-2 : 7-*dihydro*-4′ : 1″-*dimethoxy*-3 : 4-5 : 6-*dibenzazepinium Iodide* (VII).—2 : 2′-Bisbromomethyl-6 : 6′-dimethoxydiphenyl (Hall and Turner, *loc. cit.*) (70 g., 1 mol.) was dissolved in warm benzene (30 c.c.), and diethylamine (2·8 g., 2·2 mols.) added. The quaternary bromide separated almost immediately, and precipitation was completed by addition of light petroleum. The bromide was filtered off, dissolved in water, in which it was very soluble, and reprecipitated as the iodide by the addition of hot aqueous potassium iodide. 1 : 1-*Diethyl*-2 : 7-*dihydro*-4′ : 1″-*dimethoxy*-3 : 4-5 : 6-*dibenzazepinium iodide* (5·9 g., 77%) crystallised from water in rectangular plates (Found : I, 28·7. $C_{20}H_{26}O_2NI$ requires I, 28·9%).

1 : 1-*Diethyl*-2 : 7-*dihydro*-4′ : 1″-*dimethoxy*-3 : 4-5 : 6-*dibenzazepinium* (+)-*camphorsulphonate* was prepared in aqueous solution. Evaporation of the filtered solution gave a syrup which eventually crystallised in the presence of ethyl acetate. The salt (4·3 g.) was first recrystallised from acetone but could not again be obtained crystalline from this solvent. It was then crystallised from a mixture of ethyl propionate and ethyl acetate, the salt obtained almost certainly containing ethyl acetate of crystallisation; this was readily lost during short drying *in vacuo* and after such treatment the salt had m. p. 218°, $[\alpha]_{5461}^{21}$ + 22·3°, $[\alpha]_{5791}^{21}$ +19·2° (*c*, 0·9635 in ethanol) (Found : C, 66·0; H, 7·4. $C_{30}H_{41}O_6NS$ requires C, 66·3; H, 7·6%). There was no indication of separation of diastereoisomerides from this solvent and the various crops were therefore combined and crystallised by dissolving them in benzene containing a little methanol and boiling off the methanol to the point of turbidity. The salt again appeared to be solvated but the solvent was readily lost *in vacuo* and the unsolvated salt had m. p. 218°, $[\alpha]_{5461}^{21}$ +22·5°, $[\alpha]_{5791}^{21}$ +19·8° (*c*, 1·0875 in ethanol) (Found : C, 65·8; H, 7·4%). There was no change in specific rotation on further fractional crystallisation, and as the salt frequently separated first as a gum it was finally abandoned.

2 : 7-*Dihydro*-4′ : 1″-*dimethoxy*-3 : 4-5 : 6-*dibenzazepinium*-1-spiro-1‴-*piperidinium Bromide* (VIII).—2 : 2′-Bisbromomethyl-6 : 6′-dimethoxydiphenyl (21 g., 1 mol.) was dissolved in warm benzene (120 c.c.), and piperidine (9·8 g., 2·2 mols.) added. After 1 hour the benzene was decanted, and the residual gum washed with light petroleum. On the addition of a little water the gum crystallised and was filtered off at 0°. The *bromide dihydrate* (19 g., 82%), recrystallised

from water (with ice-cooling), had m. p. 114° (rhombic plates) (Found: Br, 17·8. $C_{21}H_{26}O_2NBr,2H_2O$ requires Br, 18·15%). It tended to effloresce on air-drying.

(−)-2 : 7-*Dihydro*-4′ : 1″-*dimethoxy*-3 : 4-5 :6-*dibenzazepinium*-1-spiro-1‴-*piperidinium* (+)-*Camphorsulphonate*.—The above bromide was treated with silver (+)-camphorsulphonate in aqueous solution, and the filtered solution evaporated to dryness. The residue was crystallised from acetone, and the salt obtained (25 g.) subjected to repeated fractional crystallisations from small volumes of acetonitrile. In this way 1·25 g. of the less soluble (−)-2 : 7-*dihydro*-4′ : 1″-*dimethoxy*-3 : 4-5 : 6-*dibenzazepinium*-1-spiro-1‴-*piperidinium* (+)-*camphorsulphonate* were obtained and had m. p. 248—250°, $[\alpha]_{5461}^{21}$ +19·0°, $[\alpha]_{5791}^{21}$ +15·8° (*c*, 1·105 in ethanol) (Found: C, 67·5; H, 7·3. $C_{31}H_{41}O_6NS$ requires C, 67·0; H, 7·4%).

(−)-*Dihydro*-4′ : 1″-*dimethoxy*-3 : 4-5 : 6-*dibenzazepinium*-1-spiro-1‴-*piperidinium Iodide*.—Treatment of an aqueous solution of the above camphorsulphonate with saturated potassium iodide solution gave a precipitate of (−)-2 : 7-*dihydro*-4′ : 1″-*dimethoxy*-3 : 4-5 : 6-*dibenzazepinium*-1-spiro-1‴-*piperidinium iodide*; crystallised from ethanol, this had $[\alpha]_{5461}^{22}$ −3·8° ± 0·2°, $[\alpha]_{5791}^{22}$ −3·4° ± 0·2° (*c*, 2·3485 in acetonitrile) (Found: C, 56·3; H, 5·9; I, 28·5. $C_{21}H_{26}O_2NI$ requires C, 55·9; H, 5·8; I, 28·1%).

(+)-2 : 7-*Dihydro*-4′ : 1″-*dimethoxy*-3 : 4-5 : 6-*dibenzazepinium*-1-spiro-1‴-*piperidinium* (−)-*Camphorsulphonate*.—The more soluble (+)-camphorsulphonate was obtained with $[\alpha]_{5461}^{20}$ +24·7°, $[\alpha]_{5791}^{20}$ +20·8° (*c*, 1·1 in ethanol), and gave an iodide with $[\alpha]_{5461}^{18}$ + 1·3° (*c*, 3·58 in acetonitrile) but was too soluble in acetonitrile to be further purified. Accordingly all the (+)-camphorsulphonate with $[\alpha]_{5461} > +23·5°$ was converted into the iodide and thence into the (−)-camphorsulphonate. The silver (−)-camphorsulphonate used had a slightly lower specific rotation than the silver (+)-camphorsulphonate ($[\alpha]_{5461}^{19}$ −18·3°, $[\alpha]_{5461}^{19}$ +19·7°, both 1% solutions in water) and recrystallisation of the salt made from it gave 0·7 g. of (+)-2 : 7-*dihydro*-4′ : 1″-*dimethoxy*-3 : 4-5 : 6-*dibenzazepinium*-1-spiro-1‴-*piperidinium* (−)-*camphorsulphonate* with m. p. 245—248°, $[\alpha]_{5461}^{18}$ −14·5°, $[\alpha]_{5791}^{18}$ −12·0° (*c*, 1·063 in ethanol) (Found: C, 67·4; H, 7·3. $C_{31}H_{41}O_6NS$ requires C, 67·0; H, 7·4%).

(+)-2 : 7-*Dihydro*-4′ : 1″-*dimethoxy*-3 : 4-5 : 6-*dibenzazepinium*-1-spiro-1‴-*piperidinium Iodide*.—Treatment of an aqueous solution of the above (−)-camphorsulphonate with saturated potassium iodide solution gave a precipitate of (+)-2 : 7-*dihydro*-4′ : 1″-*dimethoxy*-3 : 4-5 : 6-*dibenzazepinium*-1-spiro-1‴-*piperidinium iodide*. It was crystallised from ethanol and had $[\alpha]_{5461}^{22}$ +4·0° ± 0·4°, $[\alpha]_{5791}^{22}$ +3·6° ± 0·4° (*c*, 1·1135 in acetonitrile) (Found: C, 55·6; H, 5·9. $C_{21}H_{26}O_2NI$ requires C, 55·9; H, 5·8%).

During this resolution no fewer than 84 crops of camphorsulphonates were examined polarimetrically.

Dimorphism of the (+)- *and* (−)-*Iodides*.—The m. p.s of the active iodides (as taken by the capillary-tube method) were not sharp and underwent large changes on recrystallisation both from ethanol and from water. The m. p.s were then taken under a microscope on a Kofler heating stage and two distinct crystalline forms were recognisable. One form consisted of hexagonal plates, m. p. 215—218°, and the other of irregular prisms which macroscopically appeared sometimes as plates and sometimes as rods, and had m. p. 242—245°. Frequently, crystallisation gave mixtures of the two forms, which were readily distinguishable under the microscope and melted separately at the respective temperatures given above.

Racemisation of the (−)-*Iodide*.—The iodide with $[\alpha]_{5461}^{22}$ −2·9° was boiled under reflux in *cyclo*hexanol (b. p. 160°) solution for 8 hours and then precipitated with ether. The specific rotation was then $[\alpha]_{5461}^{19}$ −0·6°; after being boiled for a further 8 hours in *cyclo*hexanol the recovered iodide was inactive.

We are grateful to Miss G. Hilldrith for a gift of 2 : 7-dihydro-3 : 4-5 : 6-dibenzoxepin and to Dr. E. R. Holiday for spectroscopic facilities. We thank Imperial Chemical Industries Limited for a grant.

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157. *Experiments on the Synthesis of the Pyrethrins. Part VIII.* Stereochemistry of Jasmone and Identity of Dihydropyrethrone.*

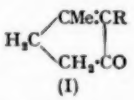
By Leslie Crombie and Stanley H. Harper.

Five 3-methyl-2-*n*-pentenyl*cyclo*pent-2-en-1-ones having the structures possible for dihydropyrethrone, a degradation product of pyrethrolone, have been synthesised. Two of these, the *cis*- and *trans*-*n*-pent-2′-enyl ketones, are the previously unrecognised *cis*- and *trans*-forms of jasmone. Natural jasmone from *Jasminum grandiflorum* is shown to be the *cis*-ketone. The configurations assigned are based on the modes of synthesis and on infra-red spectra. Comment is made on the stereochemistry of synthetic jasmones previously described in the literature. The *cis*- and *trans*-*n*-pent-3′-enyl and *n*-pent-4′-enyl structures are excluded for dihydropyrethrone, which must be *cis*- or *trans*-jasmone.

(±)-*n*-Pent-4-enylrethrolone has also been synthesised and converted into its (±)-*cis*- and (±)-*trans*-chrysanthemic esters, for assessment of their insecticidal potencies.

When pyrethrone (I*a*; the evidence for this structure is summarised in Part VII,* and references are cited therein) is catalytically hydrogenated addition of one mol. of hydrogen was found by LaForge and Haller (*J. Org. Chem.*, 1938, **2**, 546) to give a mixture of tetrahydropyrethrone (dihydrojasmone) (I*i*) and starting material. However, addition of one mol. of hydrogen bromide followed by zinc reduction yielded dihydropyrethrone, which was characterised by a semicarbazone (m. p. 202°). The same compound was obtained by West (*J.*, 1945, 412) by reduction of pyrethrolone with aluminium amalgam. Dihydropyrethrone semicarbazone gave dihydrojasmone semicarbazone on hydrogenation, but LaForge and Haller stated that it was not identical with jasmone semicarbazone, although no mixed melting point was recorded. Their experiments favoured structures (I*d*) or (I*e*) for dihydropyrethrone which West supported. For a variety of reasons (cf. Crombie, Edgar, Harper, Lowe, and Thompson, Part V, *J.*, 1950, 3552, and below) we regarded this assignment as improbable and the non-identity with jasmone as unproven.

(I*a*; R = CH_2·CH:CH·CH:CH_2-*cis*)
(I*b*; R = CH_2·CH:CH·CH_2·CH_3-*cis*)
(I*c*; R = CH_2·CH:CH·CH_2·CH_3-*trans*)
(I*d*; R = CH_2·CH_2·CH:CH·CH_3-*cis*)
(I*e*; R = CH_2·CH_2·CH:CH·CH_3-*trans*)



(I)

(I*f*; R = CH_2·CH_2·CH_2·CH:CH_2)
(I*g* R = CH:CH·CH_2·CH_2·CH_3-*cis*)
(I*h*; R = CH:CH·CH_2·CH_2·CH_3-*trans*)
(I*i*; R = CH_3·CH_2·CH_2·CH_2·CH_3)

Of the seven structures (I*b*—*h*) possible for dihydropyrethrone the cross-conjugated structures (I*g*) and (I*h*) are eliminated by West's light-absorption results. Structure (I*f*) is also excluded, for G.P. 658 920 (Heine A. G.) describes 3-methyl-2-*n*-pent-4′-enyl*cyclo*pent-2-en-1-one semicarbazone, prepared by an unstated method, as having m. p. 164—165°. Hence in an attempt to elucidate the structure of dihydropyrethrone we have synthesised the remaining four ketones (I*b*—*e*). Ketones (I*b*) and (I*c*) are of additional interest as they are the *cis*- and *trans*-forms of jasmone, which occurs in the essential oil of *Jasminum grandiflorum*, and whose stereochemistry has been in a state of confusion. Jasmone has been synthesised by Treff and Werner (*Ber.*, 1935, **68**, 640) and by Hunsdiecker (*Ber.*, 1942, **75**, 460) and the specimens obtained were all claimed to be identical with the natural ketone, the criterion of identity being the mixed melting point of the semicarbazones. Consideration of the methods used for the synthesis of the *n*-pent-2-enyl side-chain indicated that, in fact, the configuration was not the same in each case and as a corollary to our main purpose we have clarified the stereochemistry of jasmone.

* Part VII, *J.*, 1951, 2906.

n-Pent-2-enyl bromide was prepared by Bouis's procedure (*Ann. Chim.*, 1928, **9**, 403), as follows, and converted into *n*-hept-4-enoic acid* by ethyl malonate chain extension:

$$MgEtBr + CH_2{:}CH{\cdot}CHO \longrightarrow Et{\cdot}CH(OH){\cdot}CH{:}CH_2 \xrightarrow{PBr_3} Et{\cdot}CH{:}CH{\cdot}CH_2Br \xrightarrow{3\ stages} Et{\cdot}CH{:}CH{\cdot}CH_2{\cdot}CH_2{\cdot}CO_2H$$

This halide has the *trans*-configuration for Grédy (*Bull. Soc. chim.*, 1936, **3**, 1093, 1101; 1937, **4**, 415) has shown on Raman spectroscopic evidence that this is the configuration of halides prepared by the Bouis rearrangement. It is likely that this configuration would be retained in the subsequent reaction with ethyl sodiomalonate. Hence the resultant *n*-hept-4-enoic acid should have the *trans*-configuration. This is supported by the infra-red spectrum of the acid which shows strong absorption at 10·3 μ (cf. Crombie and Harper, *J.*, 1950, 873) and by its non-identity with *cis*-*n*-hept-4-enoic acid (see below). *trans*-*n*-Hept-4-enoic acid was converted into *trans*-jasmone (Ic) by the following generalised route which is known not to cause stereomutation (Harper, Part II, *J.*, 1946, 829; Crombie and Harper, Part IV, *J.*, 1950, 1152; Part V, *loc. cit.*):

$$R{\cdot}CH_2{\cdot}CO_2H \xrightarrow{SOCl_2} R{\cdot}CH_2{\cdot}COCl \xrightarrow[-EtOH]{CHNaAc{\cdot}CO_2Et} R{\cdot}CH_2{\cdot}CO{\cdot}CHAc{\cdot}CO_2Et \xrightarrow[-MeOH]{NaOMe}$$

$$R{\cdot}CH_2{\cdot}CO{\cdot}CH_2{\cdot}CO_2Me \xrightarrow[CH_2Br{\cdot}COMe]{Na\text{–}Et_2O,\ then} R{\cdot}CH_2{\cdot}CO{\cdot}CH(CO_2Me){\cdot}CH_2{\cdot}COMe \xrightarrow{aq.\ NaOH} (I)$$

A second specimen of *trans*-jasmone was prepared by this route from the *n*-hept-4-enoic acid prepared from the predominantly *trans*-*n*-hex-3-en-1-ol obtained on ring scission of the mixed *cis*- and *trans*-3-chloro-2-ethyltetrahydrofurans (Crombie and Harper, *J.*, 1950, 1715). A third specimen of *trans*-jasmone, identical with the above (mixed m. p.s), was prepared from *trans*-*n*-pent-2-enyl bromide by the following sequence (cf. Part V, *loc. cit.*):

$$Et{\cdot}CH{:}CH{\cdot}CH_2Br \xrightarrow[-EtOH]{CHNaAc{\cdot}CO_2Et} Et{\cdot}CH{:}CH{\cdot}CH_2{\cdot}CHAc{\cdot}CO_2Et \xrightarrow{aq.\ NaOH}$$

$$Et{\cdot}CH{:}CH{\cdot}CH_2{\cdot}CH_2{\cdot}COMe \xrightarrow[-Et_2O]{NaH\text{–}Et_2CO_3} Et{\cdot}CH{:}CH{\cdot}CH_2{\cdot}CH_2{\cdot}CO{\cdot}CH_2{\cdot}CO_2Et \xrightarrow[then\ CH_2Br{\cdot}COMe]{Na\text{–}Et_2O,}$$

$$Et{\cdot}CH{:}CH{\cdot}CH_2{\cdot}CH_2{\cdot}CO{\cdot}CH(CO_2Et){\cdot}CH_2{\cdot}COMe \xrightarrow{aq.\ NaOH} (Ic)$$

As the intermediary *trans*-*n*-oct-5-en-2-one showed some absorption at 10·93 μ, as well as that expected at 10·33 μ, the possibility of contamination with 4-ethylhex-5-en-2-one (*i.e.*, vinyl absorption) derived from the secondary form of the bromide, could not be discounted at this stage. Nevertheless the infra-red spectrum of the *trans*-jasmone (see figure) obtained from it shows the virtual absence of any branched-chain isomer containing a vinyl group, whilst the strong absorption at 10·33 μ substantiates the *trans*-configuration. Hunsdiecker prepared a specimen of jasmone by the first of the above routes and it is evident that both the intermediary *n*-hept-4-enoic acid and the final ketone had the *trans*-configuration.

We have recently shown unequivocally that "leaf alcohol" is *cis*-*n*-hex-3-en-1-ol (Crombie and Harper, *J.*, 1950, 873) which may be converted through the bromide and cyanide (cf. Crombie, Harper, Stedman, and Thompson, Part VI, *J.*, 1951, 2445) or by carboxylation of the Grignard reagent into what is evidently the previously unrecognised *cis*-*n*-hept-4-enoic acid. As expected, and in contrast to the *trans*-acid, *cis*-*n*-hept-4-enoic acid shows only slight absorption at 10·3 μ. These two acids are indistinguishable by physical properties (Table 1) and have not previously been characterised by derivatives; we now find that the anilides and *p*-bromophenacyl esters differ appreciably in melting point. *cis*-*n*-Hept-4-enoic acid was converted by the route outlined above into *cis*-jasmone (Ib).† Again the infra-red spectrum of *cis*-jasmone (see figure)

* Geneva numbering, $CO_2H = 1$.

† The odour of *cis*-jasmone, although of similar type to that of *trans*-jasmone, has an exotic subtlety which the latter does not possess. Synthetic dihydrojasmone is used as a substitute for natural jasmone but in our opinion is distinctly inferior to *cis*-jasmone.

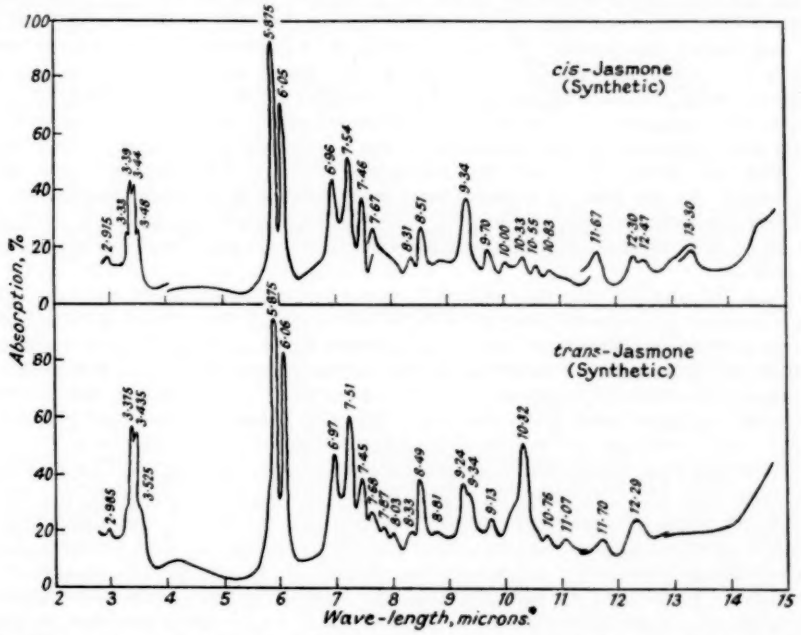
TABLE 1.

	B. p./mm.	n_D^{20}	Anilide, m. p.	*p*-Bromophenacyl ester, m. p.
cis-*n*-Hept-4-enoic acid	116°/12	1·4400	Oil *	46°
trans-*n*-Hept-4-enoic acid	105°/8	1·4400	93°	79

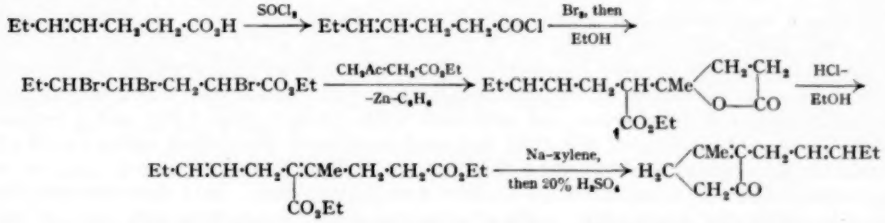
* Crystallises from light petroleum at −80°.

substantiates our stereochemical conclusion, absorption at 10·33 μ being very slight. Hunsdiecker prepared a second specimen of jasmone by this route; it was evidently *cis*-jasmone. Other infra-red structural correlations common to both isomers (cf. Parts VI and VII, *locc. cit.*) are: unsaturated aliphatic C–H stretching, 3·33; saturated C–H stretching, 3·39, 3·44, 3·48; C=O stretching, 5·875; C=C stretching, 6·05; C–H bending in CH_2 and CH_3, 6·96, 7·24 μ.

Hunsdiecker prepared further specimens of jasmone in which the side-chain double bond was introduced either by dehydration of 2-3′-hydroxy-*n*-hexyl-5-methylfuran or by



semihydrogenation of *n*-hexa-2 : 4-dien-1-ol; these were probably mainly *trans*-jasmone contaminated with structural isomers (cf. Crombie, *Quart. Reviews*, in the press). The remaining and earliest synthesis of jasmone (Treff and Werner, *loc. cit.*) utilised (*cis*-)*n*-hept-4-enoic acid, prepared from " leaf alcohol " as described above, which was converted into jasmone as follows:



* Errata in Fig.: *for* 7·54 *read* 7·24; *for* 7·51 *read* 7·21; *for* 9·13 *read* 9·73.

The bromine addition to the *cis*-acid chloride would give a substantially *threo*-4 : 5-dibromide which on debromination with zinc, during the Reformatsky reaction, would give mainly a *cis*-lactone, although some inversion of configuration is liable to occur (cf. Crombie, *loc. cit.*). Hence it is probable that Treff and Werner's product was *cis*-jasmone, possibly containing *trans*-contaminant.

It is evident (Table 2) that *cis*- and *trans*-jasmone are not distinguishable with certainty by their physical properties or by the melting points of their semicarbazones. Furthermore mixed melting points of the semicarbazones, as a criterion of non-identity, are uncertain; decomposition precedes melting and the depressions are small. In this connection it is noteworthy that although Hunsdiecker considered his preparations of jasmone identical, he observed that, as judged by their semicarbazones, the (*trans*-) jasmone prepared from *n*-pent-2-enyl bromide was "less pure" than the (*cis*-)jasmone prepared from "leaf alcohol." However the 2 : 4-dinitrophenylhydrazones differ appreciably in melting point and give well-marked depressions on admixture. Fortunately for the elucidation of the configuration of natural jasmone the 2 : 4-dinitrophenylhydrazone has been described by Naves and Grampoloff (*Helv. Chim. Acta*, 1942, **25**, 1500) and direct comparison of our synthetic 2 : 4-dinitrophenylhydrazones with a specimen kindly provided by Dr. Y.-R. Naves established unequivocally the identity of *cis*-jasmone with the natural ketone. Furthermore, within the limitations described above, direct comparison of our synthetic semicarbazones with a specimen of natural jasmone semicarbazone, kindly provided by Prof. L. Ruzicka (cf. Ruzicka and Pfeiffer, *ibid.*, 1933, **16**, 1208), bore out this conclusion. Thus "leaf alcohol" and natural jasmone each contain the *cis*-*n*-pent-2-enyl group and it is possible that the latter is formed biosynthetically from the former. Relevant to this is the isolation by Schmidt (*Chem. Ber.*, 1947, **80**, 538) of jasmone from peppermint oils previously known to contain "leaf alcohol."

Ketones (I*d*) and (I*e*), together with (I*f*), whose properties are summarised in Table 2, were synthesised from the appropriate *n*-heptenoic acids by the route generalised above. *trans*-*n*-Hept-5-enoic acid was prepared from *trans*-*n*-hex-4-en-1-ol (Crombie and Harper, *J.*, 1950, 1707), and *cis*-*n*-hept-5-enoic acid was similarly prepared from *cis*-*n*-hex-4-en-1-ol, itself obtained by semi-hydrogenation of *n*-hex-4-yn-1-ol; but a full description of these and other *n*-heptenoic acids is reserved for a future communication. Although we find that the semicarbazone of 3-methyl-2-*n*-pent-4'-enyl*cyclo*pent-2-en-1-one (I*f*) melts nearly 10° higher than recorded in G.P. 658,920 our previous conclusion is not invalidated.

Structures (I*d*) and (I*e*) must be rejected for dihydropyrethrone since the melting points of their semicarbazones are some 30° too low. By elimination, dihydropyrethrone, contrary to previous views, must be (I*b*) or (I*c*), *i.e.*, a jasmone. The recorded melting points of dihydropyrethrone semicarbazone (Table 2) do not permit of any certain stereochemical prediction, though since present evidence points to a *cis*-configuration for pyrethrone, dihydropyrethrone, a product of "1 : 2"-hydrogenation might be expected to be predominantly *cis*. Mixed melting points with derivatives of dihydropyrethrone, which would settle this point, have not been possible for the only specimen extant (that of Dr. T. F. West) had seriously deteriorated on storage and we are at present unable to undertake the lengthy reisolation of this compound.

To gain further insight into the structural features responsible for the insecticidal activity of the pyrethrins, in conjunction with Mr. R. E. Stedman, we have prepared (±)-*n*-pent-4-enylrethrolone (for an exposition of this nomenclature, see Harper, *Chem. and Ind.*, 1949, 636) and thence its esters with (±)-*cis*- and (±)-*trans*-chrysanthemic acids. Alkenylation of ethyl sodioacetoacetate with *n*-pent-4-enyl bromide (cf. route D, Part V, *loc. cit.*) followed by ketonic fission gave *n*-oct-7-en-2-one, which on carbethoxylation with ethyl carbonate and sodium hydride yielded ethyl 2-keto-*n*-oct-7-ene-1-carboxylate. Hydrolysis of this ester and condensation of the sodium salt with pyruvaldehyde in aqueous solution gave 3-hydroxy-*n*-undec-10-ene-2 : 5-dione, cyclised by aqueous sodium hydroxide to (±)-*n*-pent-4-enylrethrolone. This keto-alcohol was esterified with the appropriate acids to give (±)-*n*-pent-4-enylrethronyl (±)-*cis*- and (±)-*trans*-chrysanthemates.

TABLE 2.

		B. p./mm.	n_D^{20} *	Terminal methyl groups	$\lambda_{max.}$, Å.	ε
Naturally derived						
Dihydropyrethrone [1, 2]		115—118°/11	1·5010	1·74	2350	14 300
Jasmone [3, 4, 5, 6]		111—113°/2·5	1·4987	—	—	—
		108—110°/5	1·4997	—	—	—
		134—135°/12	—	—	—	—
Synthetic 3-*methyl*-2-n-*pentenyl*cyclo*pent*-2-*en*-1-*ones*						
cis-*n*-Pent-2′-enyl	I*b*	146°/27	1·4978	1·52	2350	12 000
trans-*n*-Pent-2′-enyl ...	I*c*	142°/23	1·4974	1·12	2340	12 300
cis-*n*-Pent-3′-enyl	I*d*	—	—	—	—	—
trans-*n*-Pent-3′-enyl ...	I*e*	130°/20	1·4946	1·67	2360	12 100
n-Pent-4′-enyl	I*f*	126°/15	1·4955	0·90	2350	13 700

		2 : 4-Dnph,† m. p.	Semicarbazone M. p.	Semicarbazone $\lambda_{max.}$, Å	Semicarbazone ε
Dihydropyrethrone [1, 2]		—	202°, 203—205°	2665	23 600
Jasmone [3, 4, 5, 6]		121·0—122·5°	204—206	—	—
		—	208	—	—
		—	210	—	—
cis-n-Pent-2′-enyl	I*b*	117·5	204—206	2650	21 900
trans-*n*-Pent-2′-enyl ...	I*c*	128·5	200—202	2650	25 700
cis-*n*-Pent-3′-enyl	I*d*	—	174—175	2660	20 000
trans-*n*-Pent-3′-enyl ...	I*e*	165	171—172	2650	22 100
n-Pent-4′-enyl	I*f*	118	173	2650	21 000

[1] LaForge and Haller, *J. Org. Chem.*, 1938, **2**, 546. [2] West, *J.*, 1945, 412. [3] Treff and Werner, *Ber.*, 1933, **66**, 1521. [4] Ruzicka and Pfeiffer, *Helv. Chim. Acta*, 1933, **16**, 1208. [5] Naves and Grampoloff, *ibid.*, 1942, **25**, 1500. [6] Specimens from *Jasminum grandiflorum*.

* n adjusted to 20°, if necessary, by means of −0·0004 per degree, within a range ±5°.

† 2 : 4-Dnph = 2 : 4-Dinitrophenylhydrazone.

EXPERIMENTAL

Most of the microanalyses, all of the terminal methyl determinations, and a few of the ultra-violet light-absorption measurements (all in purified ethanol) are by Drs. Weiler and Strauss, Oxford. The remainder were determined in the microanalytical (Mr. F. H. Oliver) and the spectrographic (Mrs. A. I. Boston) laboratories of the Organic Chemistry Dept., Imperial College. The infra-red absorption spectra were determined with a Grubb Parsons single-beam spectrometer (rock-salt prism) coupled to a Brown recorder, capillary films of pure liquids (*ca.* 5-μ thickness) being used; we are indebted to Dr. W. C. Price for this facility.

n-*Heptenoyl Chlorides.*—Thionyl chloride (1·25 mols.) was added dropwise with shaking to the *n*-heptenoic acid (1 mol.), and the mixture set aside. Next day, after brief refluxing, the heptenoyl chloride was isolated by distillation. In this way there were obtained: *cis*- (89%), b. p. 72—76°/35 mm., n_D^{20} 1·4500, and *trans*-*n*-hept-4-enoyl chloride (97%), b. p. 69—71°/12 mm., n_D^{20} 1·4473; cis- (93%); b. p. 65°/11 mm., n_D^{20} 1·4417 (Found: Cl, 24·2. $C_7H_{11}OCl$ requires Cl, 24·2%), and trans-n-*hept*-5-*enoyl chloride* (80%), b. p. 65·5—68°/16 mm., n_D^{20} 1·4490 (Found: C, 57·8; H, 7·75. $C_7H_{11}OCl$ requires C, 57·35; H, 7·55%); and *n*-hept-6-enoyl chloride (94%), b. p. 69°/17 mm.

Methyl 2-*Keto*-n-*octene*-1-*carboxylates.*—By the procedure of Part II (*J.*, 1946, 892) the heptenoyl chloride was treated with ethyl sodioacetoacetate, prepared from powdered sodium or sodium hydride, in ether and the undistilled ethyl 2 : 4-diketo-*n*-decene-3-carboxylate so formed was treated with methanolic sodium methoxide, to give the methyl 2-keto-*n*-octene-1-carboxylate. In this way there were obtained: methyl 2-keto-*cis*-, b. p. 131—137°/30 mm., n_D^{20} 1·4524, and methyl 2-keto-*trans*-*n*-oct-5-ene-1-carboxylate (56%), b. p. 109—115°/7 mm., n_D^{20} 1·4488; *methyl* 2-*keto*-cis- (43%), b. p. 122—126°/15 mm., n_D^{20} 1·4436 (Found: C, 65·05; H, 9·2. $C_{10}H_{16}O_3$ requires C, 65·2; H, 8·75%), and *methyl* 2-*keto*-trans-n-*oct*-6-*ene*-1-*carboxylate* (46%), b. p. 90—94°/0·85 mm., n_D^{20} 1·4472 (Found: C, 64·9; H, 8·7%); and *methyl* 2-*keto*-n-*oct*-7-*ene*-1-*carboxylate* (56%), b. p. 95—102°/0·5 mm. (Found: C, 65·5; H, 8·9%). Each of these keto-esters gave a deep red colour with alcoholic ferric chloride.

trans-n-*Oct*-5-*en*-2-*one.*—*trans*-*n*-Pent-2-enyl bromide (75 g.; b. p. 69—74°/114 mm.; prepared by Bouis's procedure, *Ann. Chim.*, 1928, **9**, 403) was treated with ethanolic ethyl sodioacetoacetate, by the procedure of route D (Part V, *J.*, 1950, 3552), to give after ketonic hydrolysis trans-n-*oct*-5-*en*-2-*one* (28 g.), b.p. 169—173°, n_D^{20} 1·4316 (Found: C, 76·4; H, 11·2.

$C_8H_{14}O$ requires C, 76·15; H, 11·2%). The 2 : 4-*dinitrophenylhydrazone* formed orange-red needles (from ethanol), m. p. 60° (Found : C, 55·55; H, 6·0; N, 18·75. $C_{14}H_{18}O_4N_4$ requires C, 54·9; H, 5·9; N, 18·3%).

Ethyl 2-Keto-trans-n-*oct*-5-*ene*-1-*carboxylate*.—As further described in Part V, *trans-n*-oct-5-en-2-one was caused to interact with sodium hydride and ethyl carbonate in ether, to give ethyl 2-keto-*trans-n*-oct-5-ene-1-carboxylate (62%), b. p. 69—76°/0·05 mm., n_D^{20} 1·4488.

3-*Methyl*-2-*n-pentenyl*cyclo*pent*-2-*en*-1-*ones*.—By the procedure of Part II the methyl or ethyl sodio-2-keto-*n*-octene-1-carboxylate, prepared with powdered sodium or sodium hydride in ether, was treated with bromoacetone, and the crude 2 : 5-diketo-*n*-undecene-4-carboxylic ester so formed was stirred in aqueous sodium hydroxide, to give the 3-methyl-2-*n*-pentenyl*cyclo*pent-2-en-1-one, isolated by distillation. The crude ketones (40—60% yields) obtained in this way were converted into their semicarbazones in pyridine–ethanol and these were recrystallised from ethanol. In this way there were obtained : cis-, prisms or small plates (Found : C, 65·8; H, 8·6. $C_{12}H_{19}ON_3$ requires C, 65·1; H, 8·65%), and trans-*jasmone semicarbazone*, needles, the specimen prepared from *trans-n*-pent-2-enyl bromide *via trans-n*-hept-4-enoic acid having m. p. 200°, that prepared from "*trans*"-*n*-hex-3-en-1-ol *via* "*trans*"-*n*-hept-4-enoic acid having m. p. 204° after softening at 199° (Found : C, 65·5; H, 8·7; N, 19·0; 1·71 terminal Me. $C_{12}H_{19}ON_3$ requires N, 19·0%), and that prepared from *trans-n*-oct-5-en-2-one having m. p 200—202° when crystallised from methanol (Found : C, 65·05; H, 8·55%; 1·21 terminal Me); together with 3-*methyl*-2-cis- (Found : C, 65·4; H, 8·95%; 1·42 terminal Me), and 3-*methyl*-2-trans-n-*pent*-3′-*enyl*cyclo*pent*-2-*en*-1-*one semicarbazone*, iridescent plates (Found : C, 64·9; H, 8·65%); and 3-*methyl*-2-n-*pent*-4′-*enyl*cyclo*pent*-2-*en*-1-*one semicarbazone* (Found : C, 65·05; H, 8·55%). Further data are given in Table 2. The semicarbazones, in capillary tubes, were placed in a bath at 160° which was heated rapidly (6—7° per minute) to minimise decomposition; even so the jasmone semicarbazones became yellow before melting and fused to a brown liquid. The other semicarbazones melted without decomposition. Distinctly lower m. p.s were observed microscopically on a Kofler hot stage.

The 3-methyl-2-*n*-pentenyl*cyclo*pent-2-en-1-ones were regenerated from their semicarbazones by the procedure of Part II in 81—90% yield, and portions converted into the 2 : 4-dinitrophenylhydrazones. In this way there were obtained : cis-*jasmone* (Found : C, 80·5; H, 9·8. $C_{11}H_{16}O$ requires C, 80·45; H, 9·8%), 2 : 4-*dinitrophenylhydrazone* (Found : C, 59·3; H, 5·9; N, 16·2. $C_{17}H_{20}O_4N_4$ requires C, 59·0; H, 5·85; N, 16·25%); trans-*jasmone* (Found : C, 80·3; H, 9·6%), 2 : 4-*dinitrophenylhydrazone* (Found : C, 59·4; H, 5·85; N, 16·1%); 3-*methyl*-2-trans-n-*pent*-3′-*enyl*cyclo*pent*-2-*en*-1-*one* (Found : C, 79·7; H, 9·95%), 2 : 4-*dinitrophenylhydrazone* (Found : C, 59·3; H, 5·85%), and 3-*methyl*-2-n-*pent*-4′-*enyl*cyclo*pent*-2-*en*-1-*one* (Found : C, 79·65; H, 9·8%), 2 : 4-*dinitrophenylhydrazone* (Found : C, 59·35; H, 5·65%). Further properties are given in Table 2. As the preparation of 3-methyl-2-cis-*n*-pent-3′-enyl*cyclo*pent-2-en-1-one was carried out on a small scale, insufficient of its semicarbazone was obtained to permit of regeneration; the crude ketone had b. p. 120—122°/12 mm.

Mixed m. p.s of jasmone derivatives.

		1 : 1 Mixture	
Semicarbazones, m. p.	*trans*-, 200—202°	197—200°	*cis*-, 204—206°
Semicarbazones, m. p.*	natural, 200—202°	197—198°	*cis*-, 197°
2 : 4-Dinitrophenylhydrazones, m. p.	*trans*-, 128·5°	111°	*cis*-, 117·5°
2 : 4-Dinitrophenylhydrazones, m. p.	natural, 119·5°	117—118°	*cis*-, 117°
2 : 4-Dinitrophenylhydrazones, m. p.	natural, 119·5°	110—112°	*trans*-, 128·5°

* Determined by placing the specimen on a Kofler hot stage at 170° and heating it with the rheostat at the 250° calibration. The other mixed m. p.s were determined in capillaries as described above.

(±)-n-*Pent*-4-*enylrethrolone* (4-*Hydroxy*-3-*methyl*-2-n-*pent*-4′-*enyl*cyclo*pent*-2-*en*-1-*one*) (with Mr. R. E. Stedman).—Interaction, by the procedure of route D (Part V, *loc. cit.*), of *n*-pent-4-enyl bromide (167 g.) and ethyl sodioacetoacetate, prepared from ethyl acetoacetate (148 g.) and sodium (27 g.) in ethanol (450 ml.), followed by treatment with 5% aqueous sodium hydroxide (1 l.), yielded n-*oct*-7-*en*-2-*one* (61·5 g., 58%), b. p. 172—179°, n_D^{15} 1·4324 (Found : C, 76·15; H, 11·25. $C_8H_{14}O$ requires C, 75·15; H, 11·2%). The yellow 2 : 4-*dinitrophenylhydrazone* had m. p. 65° (Found : C, 54·7; H, 5·9. $C_{14}H_{18}O_4N_4$ requires C, 54·9; H, 5·9%).

Addition of *n*-oct-7-en-2-one (30 g.) to sodium hydride (12 g.) and ethyl carbonate (59 g.) in refluxing ether (90 ml.) and then proceeding as in Part V gave *ethyl* 2-*keto*-n-*oct*-7-*ene*-1-*carboxylate* (25·5 g., 53%), b. p. 94—100°/0·6 mm., n_D^{20} 1·445—1·450 (Found : C, 66·95; H, 9·4. $C_{11}H_{18}O_3$ requires C, 66·7; H, 9·15%).

Hydrolysis of this keto-ester (27 g.) with 3% aqueous sodium hydroxide (200 ml.) during 24 hours, followed by condensation with aqueous pyruvaldehyde (42 ml.) by the procedure of Part V, yielded 3-*hydroxy*-n-*undec*-10-*ene*-2 : 5-*dione* (16·0 g., 55%), b. p. 120—127°/0·1 mm., n_D^{20} 1·466—1·471 (Found : C, 67·25; H, 9·25. $C_{11}H_{18}O_3$ requires C, 66·7; H, 9·15%).

3-Hydroxy-*n*-undec-10-ene-2 : 5-dione (16 g.) was stirred with 3% aqueous sodium hydroxide (100 ml.) during 1 hour and the product isolated by the procedure of Part V. Fractional distillation at 0·1 mm., as described, then gave (±)-n-*pent*-4-*enylrethrolone* (5·2 g., 32%), b. p. 126—134°/0·1 mm., n_D^{20} 1·504—1·505 (Found : C, 73·3; H, 9·05. $C_{11}H_{14}O_2$ requires C, 73·2; H, 8·95%).

Ozonisation of (±)-*n*-pent-4-enylrethrolone (150 mg.), by the procedure of Part VII (*J.*, 1951, 2906), yielded the formaldehyde dimedon derivative, m. p. 187—188° after one crystallisation from 50% aqueous ethanol.

(±)-n-*Pent*-4-*enylrethronyl Chrysanthemates* (with Mr. R. E. Stedman).—By the procedure of Part V (*loc. cit.*) the undistilled chloride from (±)-*trans*-chrysanthemic acid (1·2 g.) was caused to interact with (±)-*n*-pent-4-enylrethrolone (1·6 g.) and pyridine (1 ml.) in benzene (20 ml.). Distillation as described (Part V) gave (±)-n-*pent*-4-*enylrethronyl* (±)-trans-*chrysanthemate* (1·46 g., 61%), b. p. 154—164°/5 × 10^{-3} mm., n_D^{20} 1·5023—1·5026 (Found : C, 76·75; H, 9·5. $C_{21}H_{30}O_3$ requires C, 76·35; H, 9·4%).

In a similar manner interaction of the undistilled chloride from (±)-*cis*-chrysanthemic acid (1·7 g.) and (±)-*n*-pent-4-enylrethrolone (1·9 g.) gave (±)-n-*pent*-4-*enylrethronyl* (±)-cis-*chrysanthemate* (2·1 g., 62%), b. p. 152—161°/1 × 10^{-2} mm., n_D^{20} 1·5013—1·5030 (Found : C, 75·3; H, 9·3%). In contrast to our earlier experience (Part V, but cf. Part III, *J.*, 1950, 971) (±)-*cis*-chrysanthemic acid crystallised from the forerun (0·4 g.) of this distillation on storage and was identified by its m. p. and mixed m. p.

We are indebted to Mr. D. Thompson for the preparation of the methyl 2-keto-*cis*-*n*-oct-5-ene-1-carboxylate and to the Agricultural Research Council, the Central Research Fund of the University of London, and to the Chemical Society for grants. The initial experiments of this investigation were carried out at University College, Southampton, during 1946.

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158. *Heterocyclic Fluorides from Diazonium Fluorosilicates.*

By R. D. Beaty and W. K. R. Musgrave.

The decomposition of diazonium fluorosilicates is compared with that of the diazonium fluoroborates as a means of preparing fluorides of pyridine, quinoline, and 5-methylthiazole. In two cases the results have been compared with those obtained by diazotisation of the amine in anhydrous hydrogen fluoride, followed by decomposition *in situ*, and it has been shown that in these cases Ferm and Van der Werf's conclusions (*J. Amer. Chem. Soc.*, 1950, **72**, 4809) for aromatic fluorides do not apply.

Although a considerable amount of work has been carried out on the preparation of organic fluorides by decomposition of diazonium fluoroborates (Roe, " Organic Reactions," Vol. 5, p. 193), yet in very few cases have the diazonium salts of other complex acids been used. Lange and Muller (*Ber.*, 1930, **63**, 1058) have prepared 4 : 4'-difluorodiphenyl in low yield from the corresponding diazonium fluorophosphate, and Wiley (U.S.P. 2,423,359) has described the preparation of several diazonium fluorosilicates together with that of *p*-fluorobenzoic acid (12% crude yield from the diazonium salt), and the decomposition of benzenediazonium fluorosilicate by heat, but, in the last case, did not isolate any product and made no further attempt to use the diazonium fluorosilicate for purposes other than the preparation of dyes. Hawkins and Roe (*J. Org. Chem.*, 1949, **13**, 328) decomposed the diazonium fluorosilicate of methyl 5-aminonicotinate by heating it in dry toluene and obtained a crude fluoro-compound in a yield of about 15%, and Cheek, Wiley, and Roe (*J. Amer. Chem. Soc.*, 1949, **71**, 1863) applied the method to the preparation of several aromatic fluorides. In all cases except one their yields were lower than those from the

fluoroborates, and attempts to prepare 2-fluoropyridine failed completely, it being impossible even to prepare the diazonium salt. The experiments now described are concerned only with heterocyclic compounds and differ from those of Roe *et al.* in that the diazonium fluorosilicates were decomposed either in suspension in organic liquids or in solution in inorganic acids. The best results for 2- and 3-fluoropyridine were obtained by diazotising the bases in aqueous fluorosilicic acid and decomposing the diazonium salts *in situ*. The amount of 2-fluoropyridine obtained was appreciably greater than that from the Schiemann method (Roe and Hawkins, *J. Amer. Chem. Soc.*, 1947, **69**, 2443) but when the same procedure was applied to 3-aminopyridine the reverse was the case. Trial experiments with both 2- and 3-aminopyridine, in which the process was carried out in three separate stages, indicated that the reduction in yield occurred in the conversion of the diazonium fluorosilicate into fluoro-compound. We presume that the failure of Roe *et al.* to prepare pyridine-2-diazonium fluorosilicate was due to inadequate control of the temperature of reaction or to small amounts of water in the glacial acetic acid. Its conversion, and that of pyridine-3-diazonium fluorosilicate, into fluoro-compound was best carried out in anhydrous hydrogen fluoride. Preparation of 2-fluoroquinoline and 2-fluoro-4-methylthiazole by the same method gave smaller yields than by the Schiemann reaction.

It seems probable that, except in special cases, the decomposition of the diazonium fluorosilicates is not such a good method for preparing heterocyclic fluorides as is the Schiemann method. This may be due to the fact that in the diazonium fluorosilicate there are two diazonium groups in the molecule whereas in the diazonium fluoroborates there is only one, and, if we postulate either a free-radical mechanism or an intramolecular rearrangement for the decomposition of $(RN_2)_2SiF_6$, then the two groups R may be in closer proximity than during the decomposition of RN_2BF_4. We might therefore expect more side reactions, such a polymerisation, to occur. In only one case during this series of reactions was any polymeric material (dipyridyl) identified, but the residues were not examined in detail : there may have been more highly polymerised material present.

In view of the experiments of Ferm and Van der Werf (*loc. cit.*), who state that results as good as, and in some cases better than, those obtained in the Schiemann reaction can be obtained by diazotisation of an amine in anhydrous hydrogen fluoride followed by decomposition *in situ*, the preparations of 2-fluoropyridine and 2-fluoroquinoline were carried out as they describe. In these two cases, as in that of the one heterocyclic amine which they mention, it was shown that their conclusions do not apply. For 2-aminoquinoline the amount of fluoro-compound obtained was the same as by the decomposition of the diazonium fluorosilicate in anhydrous acid but less than that obtained by the Schiemann reaction (Roe and Hawkins, *J. Amer. Chem. Soc.*, 1949, **71**, 1785), but from 2-aminopyridine the yield was considerably less than by the Schiemann reaction (*idem*, *ibid.*, 1947, **69**, 2443) or from the diazonium fluorosilicate.

Experimental

Preparation and Decomposition of Pyridine-2-diazonium Fluorosilicate Aqueous Fluorosilicic Acid.—2-Aminopyridine (10 g.) was dissolved in 30% aqueous fluorosilicic acid (35 c.c.) and cooled to 5° in ice and salt. The mixture was carefully diazotised by addition of sodium nitrite (7·4 g.) during 1½ hours, the temperature being kept below 5°, and then kept in the cold bath for 1 hour. To complete the decomposition of the diazonium fluorosilicate the reaction mixture was heated at 40—50° for 1 hour (until evolution of nitrogen ceased.) Finally, the solution was called to 0°, exactly neutralised with sodium carbonate, and extracted with ether (4 times). The ethereal solution was dried ($MgSO_4$), and the ether removed at atmospheric pressure through a short fractionating column. The residue was found on distillation to be 2-fluoropyridine (4·2 g., 42%), b. p. 124·5° (Found : F, 19·5. Calc. for C_5H_4NF; F, 19·6%). Experiments in which (*a*) more fluorosilicic acid was used, (*b*) the product was isolated by steam-distillation (Roe and Hawkins, *loc. cit.*), (*c*) diazotisation was effected by means of ethyl nitrite all gave yields of 40%. The use of nitrosylsulphuric acid as diazotising agent gave a much smaller yield (10%).

Preparation and Decomposition of Pyridine-3-diazonium Fluorosilicate in Aqueous Fluorosilicic Acid.—3-Aminopyridine (3·0 g.) was dissolved in 30% fluorosilicic acid (30 c.c.) and

the solution cooled to about 0°. It was diazotised by passage of a slow stream of ethyl nitrite for 1½ hours, and, after 1 hour at 0°, it was warmed slowly to 25° until all ethyl nitrite was removed. Exact neutralisation was effected by adding ice-cold aqueous sodium hydroxide, the solution was steam-distilled, and the distillate treated with solid sodium hydroxide until a brown oil separated. This was extracted with ether and dried ($MgSO_4$). The ethereal solution was then saturated with dry hydrogen chloride, and the ether distilled while a slow stream of hydrogen chloride was passed into the solution in the distilling flask. This prevented the 3-fluoropyridine from distilling in the ether as an azeotrope (Roe and Hawkins, *loc. cit.*, 1947). After complete removal of the ether the residue in the flask weighed 1·9 g. To this was added the calculated quantity (1·05 c.c.) of diethylamine, and the 3-fluoropyridine liberated was distilled first under reduced pressure and then under atmospheric pressure (1·1 g., 36%), b. p. 105—106° (Found: F, 19·4. Calc. for C_5H_4NF: F, 19·6%).

Fluorosilicates of 2- and 3-aminopyridine, 2-aminoquinoline, and 2-amino-4-methylthiazole were prepared by Wiley's procedure, silicon tetrafluoride being used. Titration of aqueous solutions with 0·1N-sodium hydroxide showed that they had the general formula $(RNH_2)_2,H_2SiF_6$.

Diazonium Fluorosilicates.—2-Aminopyridine fluorosilicate (10 g.) was suspended in glacial acetic acid (100 c.c.) which had been made truly anhydrous by addition of the calculated quantity of acetic anhydride. (This precaution was particularly important, otherwise hydrolysis occurred.) A slow stream of ethyl nitrite was passed in for 4 hours and the mixture was stirred at $< 20°$ (cold running water). Ether (100 c.c.) was then added and the solid was filtered off, washed with cold absolute alcohol and then ether (sodium-dried), and dried under a vacuum (9 g.). The purity was determined by the method of Schiemann and Pillarsky (*Ber.*, 1929, **62**, 3035). It was necessary to pass in ethyl nitrite for about 8 hours to obtain pure (at least 93%) pyridine-2-diazonium fluorosilicate. The other diazonium salts were obtained, at least 90% pure, by passage of ethyl nitrite for 1½—2 hours.

2-*Fluoropyridine.*—(*a*) Anhydrous hydrogen fluoride (40—50 g.) was distilled into a copper vessel containing the diazonium fluorosilicate (10 g.) and the resulting solution was poured into an autoclave. The temperature was raised to 80—85° during an hour and kept at this value for a further hour, and then the vessel was cooled to 0°. The product was transferred to a copper distillation apparatus, the excess of hydrogen fluoride removed, and the residue treated with an excess (20 c.c.) of diethylamine. After transference to glass apparatus, the excess of diethylamine and volatile products were distilled under reduced pressure. Fractionation gave 2-fluoropyridine (2·1 g., 38%), b. p. 124—126°. Extraction with ether, after treatment with diethylamine, followed by distillation led to lower yields (30%). The use of larger amounts of anhydrous hydrogen fluoride did not affect the amount of product.

(*b*) The diazonium fluorosilicate (2·5 g.) in dry trichloroethylene (25 c.c.) was refluxed until nitrogen evolution ceased and then for a further 20 minutes (about 2 hours in all). The solvent was then distilled at atmospheric pressure and shown, by sodium fusion, not to contain fluorine. Distillation of the semi-solid residue gave 2-fluoropyridine (0·1 g., 7%) and left a solid (0·2 g.) which gave a red colour with an acid solution of ferrous sulphate, and a picrate, m. p. 155—156°, and must have consisted mainly of 2 : 2′-dipyridyl. Repetition of the process in light petroleum (b. p. 60—80°) gave no 2-fluoropyridine and left a solid residue which was not examined.

After the reaction had been carried out in dioxan, the solution was saturated with hydrogen chloride while the dioxan was distilled. The residue was treated with diethylamine to decompose the hydrochloride and then fractionated first under reduced pressure and then under atmospheric pressure, to give 2-fluoropyridine in 12% yield.

(*c*) When the solutions of the diazonium fluorosilicate in either 30% aqueous fluorosilicic acid or 40% aqueous hydrofluoric acid were warmed, good yields (75%) of 2-pyridone, m. p. 105°, were obtained. It gave a 3 : 5-dibromide, m. p. 205°.

(*d*) The preparation and decomposition of the diazonium fluoride were effected, by means of anhydrous hydrogen fluoride (50 g.) and 2-aminopyridine (5 g.), as described by Ferm and Van der Werf (*loc. cit.*). After the reaction mixture had been cooled in ice, the excess of acid was neutralised with sodium carbonate, and the neutral solution extracted with ether (4 × 30 c.c.). Fractionation of the dried ($MgSO_4$) extract gave 2-fluoropyridine (1 g., 20%), b. p. 125°.

3-*Fluoropyridine.*—Decomposition in anhydrous hydrogen fluoride, the reaction being carried out as for 2-fluoropyridine except that the product was isolated by steam-distillation (Roe and Hawkins, *loc. cit.*), gave 3-fluoropyridine (13%), b. p. 107—108°. Decomposition in dioxan gave 3-fluoropyridine (7%), b. p. 107°.

Decomposition of pyridine-3-diazonium fluorosilicate in aqueous fluorosilicic acid gave 3-pyridone in good yield (60%). It gave an acetate, b. p. 210°.

2-*Fluoroquinoline.*—(*a*) A solution of quinoline-2-diazonium fluorosilicate (10 g.) in anhydrous hydrogen fluoride (*ca.* 150 g.) was heated in the autoclave for 1½ hours at 80° and, after cooling, the excess of hydrogen fluoride was distilled as previously described. The residue was cooled to 0° and treated with an excess of diethylamine (20 c.c.), and the resultant suspension extracted with ether (3 × 20 c.c.). The ethereal extract was filtered, dried ($MgSO_4$), and fractionated; 2-fluoroquinoline (1·5 g., 21%), b. p. 130°/30 mm., was obtained (Found : F, 12·7. Calc. for C_9H_6NF : F, 12·9%).

(*b*) Quinoline-2-diazonium fluoride was prepared according to the method of Ferm and Van der Werf, from anhydrous hydrogen fluoride (20 g.), 2-aminoquinoline (4 g.), and sodium nitrite (1·8 g.). The solution was heated to 60° to decompose the diazonium salt and, after neutralisation with sodium carbonate, the product was steam-distilled. The distillate was treated with sodium hydroxide, and the oil which separated was isolated and dried ($MgSO_4$). Distillation gave 2-fluoroquinoline (0·66 g., 17%), b. p. 132°/30 mm.

Preparation of 2-Fluoro-4-methylthiazole.—(i) *By the Schiemann method.* 2-Amino-4-methylthiazole (10 g.) was dissolved in 40% aqueous fluoroboric acid (40 c.c.), and the clear solution cooled to 0° in an ice-salt bath. Diazotisation was effected by slow addition of sodium nitrite (7·0 g.) and the mixture was then kept at 0° for 1 hour. After being heated to 70° for a further hour it was filtered, cooled, and extracted with ether (4 × 30 c.c.). The ethereal extract was dried ($MgSO_4$), and the ether distilled, leaving *2-fluoro-4-methylthiazole* (0·98 g.) as an orange-red crystalline solid which was soluble in benzene, light petroleum, chloroform, acetone, and alcohol. It recrystallised from water as pale yellow crystals (0·5 g., 5%), m. p. 70° (Found : F, 16·0. C_4H_4NSF requires F, 16·2%). If the reaction mixture was neutralised before being extracted with ether, the yield of product was reduced to one-third.

(ii) *From the diazonium fluorosilicate.* The diazonium salt (10 g.) was dissolved in anhydrous hydrogen fluoride (50 c.c.) and decomposed by heating it in an autoclave at 80° for 1 hour. The excess of hydrogen fluoride was then distilled off and the residue treated with an excess of diethylamine (30 c.c.) in ether (50 c.c.). The mixture was transferred to a beaker, and the ether was decanted from the crystals of diethylamine hydrofluoride. These were washed with ether (20 c.c.) three more times by decantation, and the extracts were combined and filtered. After drying ($MgSO_4$), the ether was distilled, and the residue extracted with hot water (50 c.c.). Concentration of the extract gave, on cooling, orange-red crystals of 2-fluoro-4-methylthiazole (150 mg.), m. p. 69°. Recrystallisation from water gave a pale yellow product, m. p. 70° (Found : F, 16·2%).

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159. *The Photolysis of Propaldehyde.*

By R. E. DODD.

The photodecomposition of propaldehyde vapour at temperatures of 210—450° has been studied, both steady and intermittent illumination at 3132 Å being used. A pronounced curvature in the $\log_{10} K$–$1/T$ plot and a hitherto unobserved type of curve from the sector experiments suggest two independent reaction chains in this region of temperature in which the light-induced decomposition predominates.

THE kinetics of the photodecomposition of propaldehyde have not been widely studied and the work here described was initiated in an attempt to confirm and extend the few measurements by Mitchell and Hinshelwood (*Proc. Roy. Soc.*, 1937, *A*, **159**, 32) on the high-temperature photolysis. In particular, it was supposed that the stated similarity to the high-temperature photolysis of acetaldehyde would be confirmed and that a study of the effect of intermittent illumination would yield information about the individual rate constants, as in the case of acetaldehyde (Haden and Rice, *J. Chem. Physics*, 1942,

10, 445; Lucas and Rice, *ibid.*, 1950, **18**, 993; Dodd, *Trans. Faraday Soc.*, 1951, **47**, 56). It has been found, however, that the reaction is more complex and gives evidence of two simultaneous modes of decomposition.

Experimental

The apparatus for the determination of reaction rates and the determination of the ratio $\bar{r}/r_s$ (where $\bar{r}$ is the mean rate of decomposition under intermittent illumination, and r_s the steady rate under the same conditions of temperature and pressure but uninterrupted illumination) has been described (Dodd, *loc. cit.*). Initial rates of change of total pressure were measured over the temperature range 210—450°. Analyses of residual aldehyde were made by absorption in sodium hydrogen sulphite solution and titration with iodine.

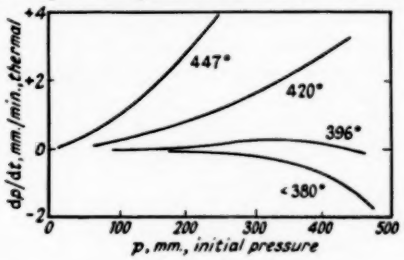
For the reaction under steady illumination, at 3132 Å, the intensities of light absorbed ($I_{abs.} \sim 10^{-11}$ $\boldsymbol{Nh\nu}$ cm.$^{-3}$ sec.$^{-1}$) were measured directly by two selenium cells, screened by 2-mm. Chance OX7 filter glass. One cell, which could be switched out of circuit, observed transmitted light while the other observed the lamp through a variable gauze screen. They were connected, in opposition, to a spot galvanometer and were balanced to zero by means of the gauze screen when the reaction vessel was evacuated. Corrections were made for transmission losses and reflection (Hill and Hunt, *J. Chem. Physics*, 1947, **15**, 111). The calibration of galvanometer reading against light absorbed was made through the photolysis of acetaldehyde, whose absolute rate constant at 200° was taken to be 41·5 mole$^{-1/2}$ cm.$^{-3/2}$ sec.$^{-1/2}$ (Grahame and Rollefson, *ibid.*, 1940, **8**, 98).

Propaldehyde from various sources was used, from redistilled technical grade to Eastman Kodak white label. Various drying and distillation procedures were adopted, but in every case redistillation immediately preceded a vacuum-distillation into the aldehyde reservoir. No differences in behaviour were detectable in the various samples.

Results

General Characteristics.—An appreciable dark reaction was observed. Initial rates of change of pressure varied with aldehyde pressure (Fig. 1) in a manner indicating a thermal

Fig. 1. *Pressure-dependence of thermal reaction at various temperatures.*



decomposition, which became appreciable at about 400°, and a competing condensation, with negligible temperature-dependence. This condensation may have occurred in the tubes leading to the reaction vessel or at the surface of the mercury manometer, though the dead space was kept at ~60°.

The reaction rate under steady illumination was appropriately corrected for dark reaction and the function

$$y = r_s \text{ (mm./min.)}/60\,p \text{ (mm.)}\, I_{abs.}^{1/2} \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad (1)$$

(expected to be constant by analogy with the acetaldehyde photolysis) was found to vary with initial pressure (see Fig. 2) according to

$$y = K - \alpha p^{1/2} \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad (2)$$

This can be accounted for on the assumption that a competing light-induced polymerisation occurs, where

$$\sigma = 60\,\alpha p^{3/2}\, I_{abs.}^{1/2} \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad (3)$$

These conclusions are supported by analysis for propaldehyde. In every case the loss of aldehyde ($-\Delta p_{ald.}$) exceeded the pressure increase ($\Delta p_{tot.}$): in the dark $-\Delta p_{ald.}/\Delta p_{tot.}$ varied

from zero at 395° (when condensation and thermal decomposition were practically balanced) to −0·55 at 310° : under illumination, $-\Delta p/\Delta p_{tot.}$ varied from 0·64 to 0·80, though 0·88 and 0·94 were obtained after prolonged (complete reaction) runs. The comparison of rates at 395° confirms the light-induced polymerisation extra to the dark condensation.

FIG. 2. *Pressure-dependence of light-induced reaction : open points correspond to half incident light intensity.*

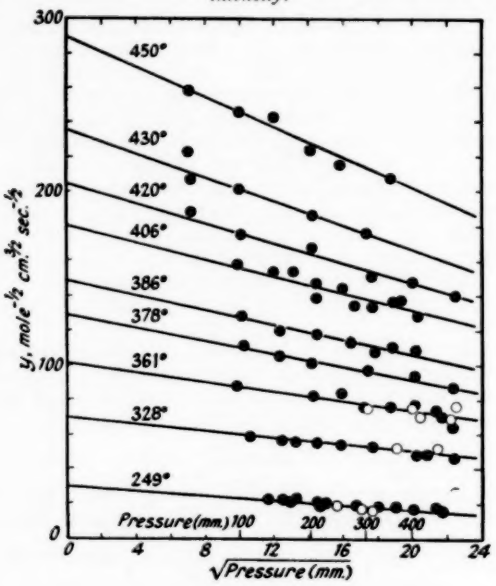
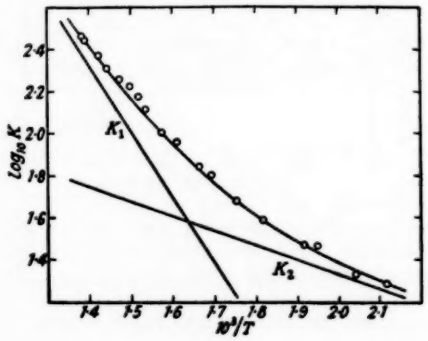


FIG. 3. *Temperature-dependence of photodecomposition.*



Photodecomposition under Steady Illumination.—The principal contribution to the rate of change of pressure in the temperature range studied was the light-induced decomposition. The y–$\sqrt{p}$ curves (Fig. 2), extrapolated to zero, give the constant K [eqn. (2)], which should be that of the pure photodecomposition (rate, r_s) obeying the equation

$$r_s = K\,[C_2H_5{\cdot}CHO]\sqrt{I_{abs.}} \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad (4)$$

That the rate was proportional to $\sqrt{I_{abs.}}$ was shown within experimental error by halving the light intensity to give the open points in Fig. 2, and was further borne out by the sector experiments at 356° and above.

The plot of $\log_{10} K$ against the reciprocal of temperature (Fig. 3) did not, however, yield a

straight line but a curve suggesting two independent contributions to the reaction. By successive approximations these were estimated as :

$$K_1 = 10^{6\cdot7 \pm 0\cdot6} \exp [(-14\cdot4 \pm 1\cdot0) \text{ kcal.}/RT]$$

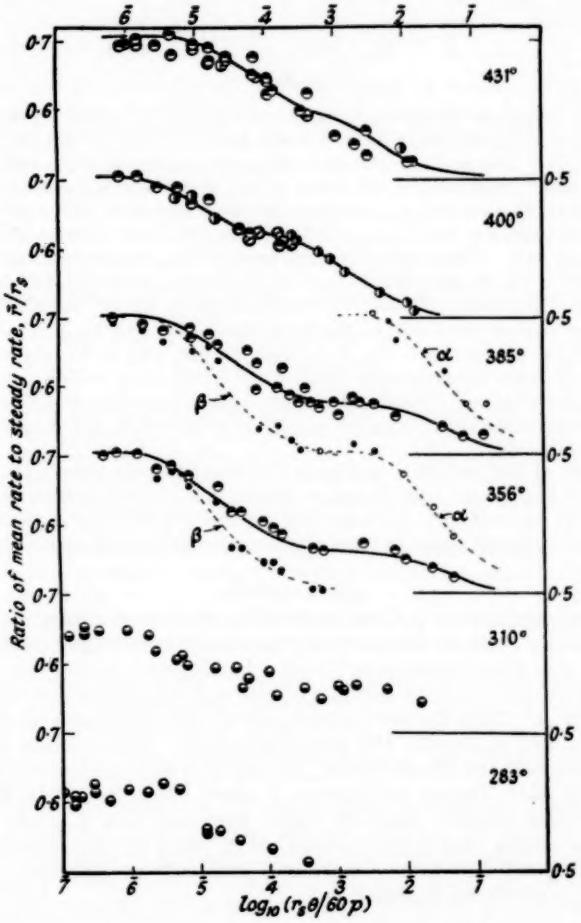
and

$$K_2 = 10^{2\cdot8 \pm 0\cdot6} \exp [(-3\cdot3 \pm 0\cdot4) \text{ kcal.}/RT]$$

where

$$K = K_1 + K_2 \quad \ldots\ldots\ldots\ldots\ldots\ldots \quad (5)$$

FIG. 4. *Sector results : $\bar{r}/r_s$ as a function of sector speed. The small points are derived values of $\bar{r}_\alpha/r_{s\alpha}$, and $\bar{r}_\beta/r_{s\beta}$ and the broken lines are fitted to them [eqn. (8)]. The full curves are calculated from fitted curves [eqn. (7)].*



Photodecomposition under Intermittent Illumination.—Equation (4) can be explained, as for acetaldehyde, by a mechanism in which one of the free radicals found in the primary step (quantum yield, k_1) induces further decomposition in a regenerative chain reaction (k_2) and is destroyed in a bimolecular terminating step (k_3). If that explanation is to hold, the ratio of mean rate to steady rate determined in sector experiments should obey the equation

$$\frac{\bar{r}}{r_s} = f\left(\frac{k_3}{k_2} \cdot \frac{r_s\theta}{60p}\right) \quad \ldots\ldots\ldots\ldots \quad (6)$$

where θ is the duration of each light or dark period.

Accordingly, the values of $\bar{r}/r_s$ for propaldehyde at various temperatures were plotted against $\log_{10}(r_s\theta/60p)$ as in Fig. 4. Though the theoretical limits of $\bar{r}/r_s$ for a reaction rate proportional to $\sqrt{I_{abs.}}$, *viz.*, $1/\sqrt{2}$ and $\frac{1}{2}$, are reached at temperatures of 356° and above, the intermediate points do not conform to the function f which is applicable to a single chain-carrying radical (Melville and Burnett, *Proc. Roy. Soc.*, 1947, *A*, **189**, 470; Dodd, *loc. cit.*).

If it is supposed that two independent contributions are made to the reaction (subscripts α and β) each obeying eqns. (4) and (6) but with different chain-carrying species of different life-times and reaction constants, then

$$\frac{\bar{r}}{r_s} = \frac{K_\alpha}{K}\cdot\frac{r_\alpha}{r_{s\alpha}} + \frac{K_\beta}{K}\cdot\frac{\bar{r}_\beta}{r_{s\beta}} \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad (7)$$

where

$$\frac{r_\alpha}{r_{s\alpha}} = \mathrm{f}\left(\frac{k_{3\alpha}}{k_{2\alpha}}\cdot\frac{r_{s\alpha}\theta}{60p}\right);\ \frac{\bar{r}_\beta}{r_{s\beta}} = \mathrm{f}\left(\frac{k_{3\beta}}{k_{2\beta}}\cdot\frac{r_{s\beta}\theta}{60p}\right) \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad (8)$$

and

$$K = K_\alpha + K_\beta \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad (9)$$

From eqn. (7) it is apparent that at such values of θ that $\bar{r}_\alpha/r_{s\alpha}$ is already at its upper limit of 0·707, while $\bar{r}_\beta/r_{s\beta}$ is still at its lower limit of 0·500, the resultant $\bar{r}/r_s$ will be constant at a value $0{\cdot}500 + 0{\cdot}207\ K_\alpha/K$. The marked plateaux at temperatures of 310°, 356°, and 385° are in accordance with this. In principle, the value of K_α, and hence K_β, can be deduced from the height of a plateau; $\bar{r}_\beta/r_{s\beta}$ and $\bar{r}_\alpha/r_{s\alpha}$ can then be calculated from the observed values of $\bar{r}/r_s$, it being assumed respectively that $\bar{r}_\alpha/r_{s\alpha} = 0{\cdot}707$ to the left of the plateau and $\bar{r}_\beta/r_{s\beta} = 0{\cdot}500$ to the right of the plateau. These ratios plotted against $\log_{10}(r_s\theta/60p)$ should now conform to function f [eqn. (8)]. Fig. 4 shows the derived ratios (smaller points) at 356° and 385°, the fitted curves (broken line) from eqn. (8), and the resultant curve for $\bar{r}/r_s$ calculated [eqn. (7)] from them. The fitted curves yield values for $\log_{10} K/\sqrt{k_1k_{3\alpha}}$ and $\log_{10} K/\sqrt{k_1k_{3\beta}}$. Hence at 356°, $K_\alpha = 28$, $K_\beta = 66$ (cf. $K_1 = 53$, $K_2 = 41$); at 385°, $K_\alpha = 45$, $K_\beta = 88$ (cf. $K_1 = 88$, $K_2 = 45$); and, at both temperatures, $k_1k_{3\alpha} = 10^{8\cdot7}$ and $k_1k_{3\beta} = 10^{15}$. It is, however, not clear how far this is fortuitous. Similar procedure applied to results at 400° and 431° enables a tolerable fit of the calculated full curve, but the found values of K_α and K_β are less in agreement with K_1 and K_2 while $k_1k_{3\alpha} = 10^{11\cdot5}$.

At temperatures of 310° and 283° (as also at 325° and 245°, not shown) the value of $\bar{r}/r_s$ does not reach 0·707 at high sector speeds (up to 3000 r.p.m., corresponding to $\sim 8 \times 10^{-4}$ sec.). This is probably too far to the left to be another plateau and therefore indicates deviation from the $\sqrt{I_{abs.}}$ law, the apparent order at these temperatures being 0·63 and 0·66.

Discussion

The sector experiments are a better indication of deviation from the square-root law at lower temperatures than are the measurements under steady illumination in which such deviation would be within experimental error; but for that reason the correction to the steady-rate results would be small and in any case not in the direction required to make a straight line of Fig. 3. Thus the evidence remains for two simultaneous reactions, obeying the same kinetics and of roughly the same magnitude. The reaction is undoubtedly a chain reaction (Mitchell and Hinshelwood, *loc. cit.*) and ethyl radicals have been detected by mirror methods (May, Taylor, and Burton, *J. Amer. Chem. Soc.*, 1941, **63**, 249; Garrison and Burton, *J. Chem. Physics*, 1942, **10**, 730). Ivin and Steacie (*Proc. Roy. Soc.*, 1951, *A*, **208**, 25) have shown that ethyl radicals react, both by disproportionation and by combination, with small activation energy and with collision efficiency approaching the maximum. This suggests mechanism β as:

$$\mathrm{C_2H_5{\cdot}CHO} + h\nu \longrightarrow \mathrm{C_2H_5} + \mathrm{CHO} \quad . \quad . \quad . \quad . \quad . \quad . \quad k_1$$

$$\mathrm{C_2H_5} + \mathrm{C_2H_5{\cdot}CHO} \longrightarrow \mathrm{C_2H_6} + \mathrm{CO} + \mathrm{C_2H_5} \quad . \quad . \quad . \quad . \quad k_{2\beta}$$

$$\mathrm{C_2H_5} + \mathrm{C_2H_5} \longrightarrow \mathrm{C_2H_6} + \mathrm{C_2H_4} \text{ and } \mathrm{C_4H_{10}} \quad . \quad . \quad . \quad k_{3\beta}$$

with the reasonable identification $K_\beta = K_1$, $k_{2\beta} \sim 10^{14} \exp(-14\ \mathrm{kcal.}/RT)$.

It may be conjectured that the other mechanism involves formyl radicals in a similar chain, though there is no direct evidence for their stability at these temperatures. Their participation in the acetaldehyde photolysis has been suggested though not confirmed (Haden and Rice, *loc. cit.*). Hydrogen atoms and "hot" molecules are also possible

species. It is possible that the latter are at least involved in the light-induced polymerisation, since eqn. (3) would be obeyed if the initiation took place according to

$$h\nu + C_2H_5{\cdot}CHO \underset{k_b}{\overset{k_a}{\rightleftharpoons}} C_2H_5{\cdot}CHO^*$$

$$C_2H_5{\cdot}CHO^* + C_2H_5{\cdot}CHO \xrightarrow{k_c} P_1, \text{ etc.}$$

if $k_b \gg k_c$, and if the termination were by mutual reaction (Gee and Melville, *Trans. Faraday Soc.*, 1944, **40**, 240).

Further speculation is not warranted by these data and it is not intended at present to continue the investigation. Yet there is good evidence for the composite mechanism in the pronounced curvature of the Arrhenius plot and in data from sector experiments of a type not previously remarked.

The author acknowledges the assistance of Mr. R. Campbell in some of the measurements, a gift of gears and other parts from Meccano Ltd., and a grant from King's College Research Committee. He is also indebted to Dr. P. L. Robinson for encouragement and facilities.

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160. *The Stability of Polyvinyl Acetate in Technical Mustard Gas Solution.*

By J. IDRIS JONES.

Solutions of vinyl acetate polymers in a technical grade of mustard gas were unstable on storage. At first the viscosity was reduced, but later it increased, the process culminating in gelation. The cause of this instability has been traced to constitutional changes in the polymer brought about by interaction with the solvent. The first phase is associated with the rupture of weak linkages in the polymer chain. Later, cross-linking with the solvent takes place, yielding an insoluble polymer. McDowell and Kenyon's evidence for the existence of weak linkages in polyvinyl acetate has been re-examined and it has been shown that when the acetate groups of the polymer are removed by hydrolysis and subsequently restored by acetylation the initial and final polymers behave differently in mustard gas solution.

VISCOSITY changes in solutions of high polymers on ageing have been frequently reported. These changes may arise from different causes, such as variations in the degree of solvation of the polymer, or in the orientation or configuration of the macromolecules in solution. Again they may be due to changes in the chemical nature of the polymer or in its molecular weight.

An investigation of the behaviour of various high polymers in mustard gas solution revealed marked differences in stability on storage (Ministry of Supply, unpublished information). Thus, polymethyl methacrylate and polystyrene solutions remained stable for prolonged periods whereas, in the cases of cellulose esters and ethers, methylated starches, and chlorinated rubber, significant changes in viscosity occurred quite rapidly. With vinyl acetate polymers an initial reduction in viscosity was observed; later the viscosity increased and this trend continued to the point of gelation. Storage in contact with metallic iron accentuated the changes. Blaikie and Crozier (*Ind. Eng. Chem.*, 1936, **28**, 1155) aged solutions of polvinyl acetate in glacial acetic acid in glass bombs at 160° and observed an initial decrease in the viscosity followed by an increase at the end of four weeks; when air was excluded the changes were not so pronounced. Morrison, Holmes, and McIntosh (*Canad. J. Res.*, 1946, **24**, *B*, 179) reported on the instability of solutions of three polymers, polyvinyl acetate, polystyrene, and polymethyl methacrylate in each of three solvents, 2 : 2′-dichlorodiethyl ether, nitrobenzene, and 2 : 2′-dichlorodiethyl sulphide;

observed variations in viscosity were traced to changes in the molecular weight of the dissolved polymers caused by the presence of small amounts of impurities; in particular, oxygen appeared to give rise to degradation reactions, whereas iron salts caused the formation of gel structures. The production of insoluble cross-linked materials from solutions of various polymers by the agency of metallic halides active in Friedel–Crafts reactions has been demonstrated by Bevington and Norrish (*J.*, 1948, 771). In the case of polystyrene in ethylene dichloride the solvent participates in the reaction, leading to a cross-linked structure with elimination of hydrogen chloride.

The present investigation was undertaken with the object of elucidating the underlying cause of instability in the polyvinyl acetate–mustard gas system. By noting changes in viscosity the stability of solutions of commercial grades of polyvinyl acetate (manufactured

FIG. 1.

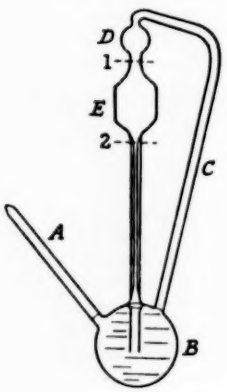
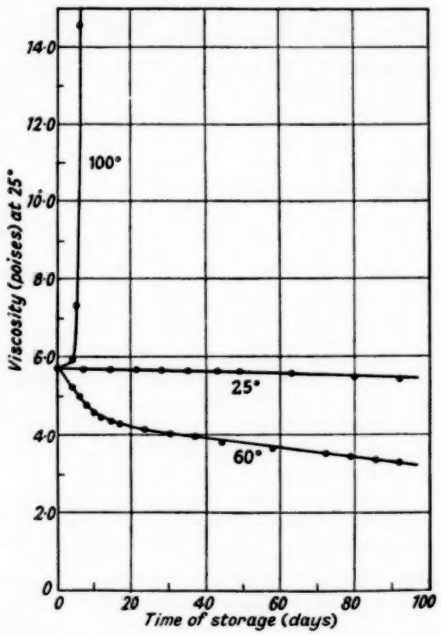


FIG. 2. *Viscosity changes of Gelva* 15 *solution on storage at* 25°, 60°, *and* 100°.



by the Shawinigan Chemical Co., Canada, and marketed under the trade name "Gelva") in mustard gas at 25°, 60°, and 100° was investigated. The mustard gas used was a commercial mixture of 60% of 2 : 2′-dichlorodiethyl sulphide and 40% of 2 : 2′-di-(2-chloroethylthio)diethyl ether by weight. A modified form of viscometer (Fig. 1) designed for dealing with vesicant liquids functioned very successfully; it was an adaptation of that used by Kuenen and Visser (Barr, "A Monograph of Viscometry," p. 123) for determining the viscosity of liquid butane. The progress of the stability tests for "Gelva 15" is shown graphically in Fig. 2. At 25° a small but steady decrease in viscosity was observed for a period of 90 days. Likewise, at 60°, the viscosity decreased, but much faster. At 100°, however, the first reading, taken after 4 days, showed a definite increase and the viscosity continued to rise sharply until, after 6 days 19 hours, the solution set to a gel. It is possible that, in the last case, a reading taken at an earlier stage might have revealed an initial phase of viscosity depression.

If the reduction in viscosity at 25° and 60° results from degradation of the polymeric molecules in contact with mustard gas, then this necessarily entails rupture of carbon–carbon

bonds if, as is generally believed, the molecules of polyvinyl acetate consist of linear chains of such carbon-to-carbon linkages. Such a rupture seems very unlikely. A more plausible explanation is to be found in McDowell and Kenyon's suggestion (*J. Amer. Chem. Soc.*, 1940, **62**, 415) that a limited number of unstable linkages are present in the polyvinyl acetate chain. These, they suggest, may be due to oxygen from peroxide catalyst, or to acetaldehyde from the vinyl acetate monomer, entering into the polymer to produce a small number of such linkages. This concept of the inclusion of oxygen in the polymer structure has also been advanced by Staudinger and Schwalbach (*Annalen*, 1931, **488**, 8). The role of oxygen in vinyl polymerisation has been discussed by Barnes (*J. Amer. Chem. Soc.*, 1945, **67**, 217); and Bovey and Kolthoff (*ibid.*, 1947, **69**, 2143) have shown that, in the case of styrene, copolymerisation with oxygen to give a 1 : 1 copolymer is possible.

FIG. 3. *Viscosity changes of reacetylated Gelva* 15 *solution on storage at* 25°, 60°, *and* 100°.

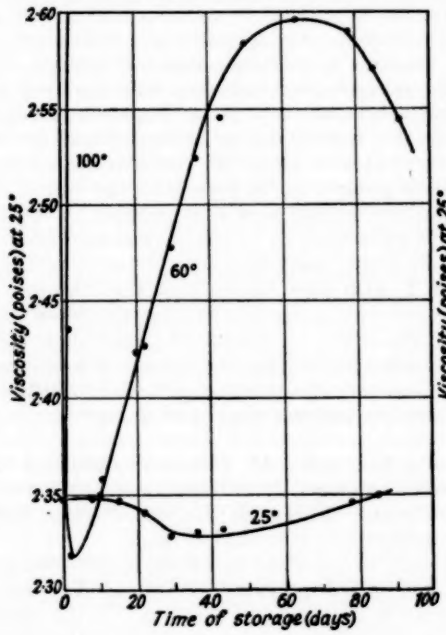
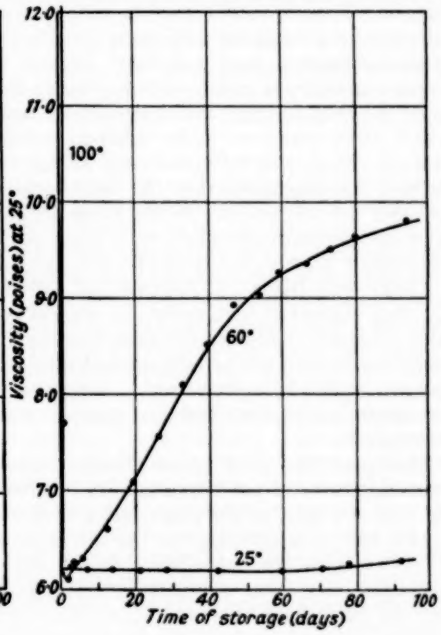


FIG. 4. *Viscosity changes of reacetylated Gelva* 45 *solution on storage at* 25°, 60°, *and* 100°.



If a limited number of such less stable linkages are present in polyvinyl acetate molecules, then the fission of these bonds would account for the observed behaviour of the polymer on the assumption that these bonds were vulnerable to mustard gas. Another reaction must be postulated to account for the marked increase in viscosity which follows the first phase of viscosity reduction.

McDowell and Kenyon's evidence for the possible existence of these unstable linkages was based on their experimental study of the molecular-weight relations in the system polyvinyl acetate ⟶ polyvinyl alcohol ⟶ polyvinyl acetate. Vinyl acetate polymers of various degrees of polymerisation were hydrolysed to polyvinyl alcohols and the latter acetylated to give polyvinyl acetates. It was found that the reacetylated polymers possessed degrees of polymerisation, as calculated from specific-viscosity measurements, which were less than those of the parent acetate polymers. This decrease of average chain length is attributed to the rupture of the less stable linkages in the macromolecules during the cycle of operations involving hydrolysis and acetylation. Certain unexplained differences in behaviour were observed between vinyl acetate polymers prepared in the

laboratory and commercial polymers of unspecified origin. It is significant that no change in chain length was observed when one sample of reacetylated polyvinyl acetate was taken round a second cycle of hydrolysis and acetylation. Blaikie and Crozier (*loc. cit.*) had made a similar observation earlier; they also observed that a certain degree of apparent breakdown of polyvinyl acetate occurs when it is milled, heated with acetic acid, or treated with hydrochloric acid.

Employing the osmotic method Staudinger and Warth (*J. pr. Chem.*, 1940, **155**, 278) have also studied the molecular-weight relations in this cycle for polyvinyl acetate fractions obtained by precipitation of a laboratory-made sample as well as for commercial preparations. With the former little change was observed, whereas a significant reduction in chain length occurred with the commercial polymers of high molecular weight. Some experiments on the hydrolysis of polyvinyl acetate samples and acid treatment of various polyvinyl alcohols have been reported by Marvel and Inskeep (*J. Amer. Chem. Soc.*, 1943, **65**, 1710) in which the chain lengths measured by viscosity methods showed marked changes. These changes were in either direction depending on experimental conditions and were very irregular and unpredictable in amount. On spectroscopic evidence these authors suggested that polyvinyl alcohol contains a terminal aldehyde group. The presence of this end-group, with its ability to undergo acetal formation with the hydroxyl groups of neighbouring molecules under acid conditions and to participate in aldol or reverse aldol reactions under alkaline conditions, is believed to be responsible for the observed changes in molecular size of polyvinyl alcohol under the conditions described. Further, it is suggested that the same aldehyde group may be present at the end of the polyvinyl acetate chain. While these suggestions explain how it is possible to prepare polymers of higher molecular weight from polyvinyl acetate by hydrolysis and reacetylation they cannot account for the reduction in chain length observed under certain conditions.

Clarke and Blout (*J. Polymer Sci.*, 1946, **1**, 419) have shown that the viscosity of polyvinyl alcohol of high molecular weight is reduced in aqueous 0·02N-hydrochloric acid and is constant only after 24 hours' heating at 90—100°. Examination of the ultra-violet absorption spectra of the polyvinyl alcohol revealed an increase in intensity of a carbonyl band as a result of this treatment. However, these carbonyl groups appeared to be ketonic; they appear to be distributed at random along the polymer chain and independently of chain length.

Thompson and Torkington (*Trans. Faraday Soc.*, 1945, **41**, 246) have examined the infra-red spectra of polyvinyl alcohol but nothing emerged from their studies that would help to throw light on the degradation of the acetate. Ellis *et al.* (*J. Chem. Physics*, 1950, **18**, 413) have also investigated the infra-red spectrum of polyvinyl alcohol.

The evidence for degradation in the sequence of reactions involving alcoholysis and acetylation has been re-examined, using commercial polyvinyl acetates. The same polymers have been used in the stability tests in mustard gas solution. If the above reactions serve to rupture the weak bonds in the polymer chain, then the reacetylated polymers would be expected to behave differently in solution in mustard gas. Fig. 3 shows the viscosity changes of mustard gas solutions of reacetylated " Gelva 15 " on ageing at 25°, 60°, and 100°. Comparison with the data presented in Fig. 2 reveals a striking difference between the behaviour of original and reacetylated polymer. Fig. 4 shows the stability of reacetylated " Gelva 45 " (a polymer of higher molecular weight) in mustard gas solution under the same conditions. The significance of these results is discussed below (p. 892).

Experimental

Three commercial polyvinyl acetates—Gelva 7, Gelva 15, and Gelva 45—manufactured by the Shawinigan Chemical Co., Canada, were used. Found, for Gelva 7, 15, and 45 respectively: C, 55·5, 55·8, 55·6; H, 7·0, 7·0, 7·0; Ac, 50·0, 49·5, 49·0. Calc. for $(C_4H_6O_2)_n$: C, 55·8; H, 7·0; Ac, 50·0%.

Hydrolysis.—Several methods have been proposed for the hydrolysis of polyvinyl acetate to polyvinyl alcohol, utilising alkaline or acid conditions. The following methods were examined and compared:

(i) *Methyl-alcoholic sodium methoxide* (Staudinger, Frey, and Starck, *Ber.*, 1927, **60**, 1782). The polyvinyl alcohol from Gelva 15 was obtained in quantitative yield as a rather yellowish powder with ash content 1·82% and entirely free from acetate groups. A nitrogen atmosphere was maintained during the reaction. Dialysis was recommended by the authors for removal of the mineral matter present in the product. In this experiment ice-cold water (500 ml.) was used to wash the product. In a second preparation, with the same proportion of reactants but with 1 litre of ice-cold water used for washing of the polyvinyl alcohol the ash content was reduced to 1·20%; again, hydrolysis was complete. There is a possibility, both on dialysis and on washing with water, that some of the more soluble species of lower molecular weight might be removed with consequent increase in apparent molecular weight. However, as will be seen later, molecular-weight determinations by viscosity negative this.

(ii) *Cold alcoholic sodium hydroxide and a dioxan solution of polyvinyl acetate* (*Gelva* 15) (Staudinger and Warth, *J. pr. Chem.*, 1940, **155**, 278). Despite the careful exclusion of air the product, obtained after washing with ice-cold water (to remove sodium acetate and excess of sodium hydroxide), was slightly yellow; its ash content was 1·10 and its residual acetyl content 1·9%.

(iii) *Alcoholic hydrogen chloride.* Dry gaseous hydrogen chloride was slowly bubbled through a boiling solution of Gelva 15 in methyl alcohol. The solution darkened considerably and the precipitated polyvinyl alcohol was of a brownish colour. Polyvinyl alcohol is known to be very susceptible to hydrochloric acid, giving a water-insoluble black modification. This method does not appear to be satisfactory.

(iv) *Absolute alcohol containing* 1% *of sulphuric acid* (U.S.P. 2 109 883). A 20% solution (100 g.) of Gelva 15 in ethyl alcohol containing 1 g. of sulphuric acid was refluxed for 16 hours. The polyvinyl alcohol precipitated was pure white and granular. It was filtered off and washed with alcohol. When dried at 100° before analysis it darkened, owing to charring by sulphuric acid retained in it. The product was taken up in water and precipitated in a large volume of alcohol. This gave a purer material but it still appeared to retain some sulphuric acid. Its acetyl content was 1·94%. It is known that the last traces of acid are difficult to remove from polyvinyl alcohol. Hermann and Haehnel (*Ber.*, 1927, **60**, 1658) distinguish between " acid " polyvinyl alcohols and " alkali " polyvinyl alcohols. Polymers obtained by hydrolysis with dilute alcoholic acid cannot be completely reacetylated (Staudinger, Frey, and Starck, *loc. cit.*). This may be due to the loss of some hydroxyl groups by removal of water. Whether this dehydration occurs during the hydrolysis or on drying has not been ascertained but there are indications that the change is accelerated by residual traces of acid (Hermann and Haehnel, G.P. 480 866/1929).

(v) *Alcoholysis with an alkaline catalyst* (Blaikie and Crozier, *loc. cit.*). Polyvinyl acetate (100 g.) in dry methanol (600 ml.) was treated with potassium hydroxide (4 g.) in dry methanol. Alcoholysis occurred and, after 24 hours at room temperature, the polymeric alcohol separated as an opaque gel. The product was isolated by dissolving the gel in hot water, cooling, and pouring the solution into acetone (4 l.) which was vigorously stirred. The alcohol separated as a pure white fibrous material. When prepared by this method polyvinyl alcohol has a low ash content and contains but little residual hydrolysable matter. It can be easily and completely reacetylated. These considerations coupled with the apparent purity of the product led to the choice of this method for the present investigations. On analysis the polyvinyl alcohols from Gelva 7, 15, and 45 respectively gave the following results. Found, after drying at 105° for 1 hour in a vacuum: Ac, 1·2, 0·9, 1·0; ash, 1·31, 1·25, 2·20%.

Reacetylation.—The polyvinyl alcohol samples were reacetylated by heating them with acetic anhydride and pyridine. The polymer (1 part) was heated on the steam-bath with a 2 : 1-mixture by volume (10 parts) of pyridine and acetic anhydride both of " AnalaR " quality. Acetylation was complete in 8 hours, the resulting acetate dissolving in the reaction mixture to form a homogeneous dope. The ester was precipitated in distilled water, washed several times with large volumes of hot water, and ultimately dried in a vacuum at 105°. The reacetylated materials possessed acetyl contents equal to those of the parent acetates [Found: Ac (for Gelva 7) 50·0, (for Gelva 15) 49·8, (for Gelva 45) 50·4%].

By the same methods of hydrolysis and esterification the three samples of reacetylated polyvinyl acetates were taken round a second cycle. Again the final polyvinyl acetates possessed acetyl contents equal to those of the original acetate.

A sample of commercial polyvinyl alcohol (RH.349; completely hydrolysed polymer, of a medium viscosity, manufactured by E.I. du Pont de Nemours & Co.) was also taken round the cycle alcohol ⟶ acetate ⟶ alcohol by the same procedure.

Molecular-weight Determinations by the Viscosity Method.—McDowell and Kenyon (*loc. cit.*)

used the Staudinger viscosity relationship to measure chain lengths of original and regenerated polyvinyl acetates. The same value was assumed for the constant for both acetate and alcohol polymers ($K_m = 2{\cdot}6 \times 10^{-4}$). In recent years Staudinger's original relationship has been largely discredited. Proved cases of disagreement with the " rule " now far outnumber the instances of agreement and various modifications have been proposed. There is evidence to show that K_m decreases as the molecular weight increases (Meyer, *Kolloid Z.*, **1941**, **95**, 70) and indeed Staudinger himself has adduced evidence indicating that this is so in the case of polyvinyl acetate and polyvinyl alcohol (Staudinger and Warth, *loc. cit.*) Further, there is no valid reason for assigning the same value to the constant for both polyvinyl acetate and alcohol.

The molecular weight of these two polymers cannot be compared in the same solvent since the alcohol is insoluble in the usual solvents for the ester and *vice versa*. Water and aqueous fatty acids are the only media in which polyvinyl alcohol can be dispersed for viscosity measurements. Formamide has been reported as a solvent for the alcohol but at ordinary temperatures the solution is too viscous for use in a viscometer. Ethylenediamine gave viscosity values which were inconsistent and irregular (Clarke and Blout, *loc. cit.*). In some cases, McDowell and Kenyon used formic acid as a solvent for the alcohol, again using the same value for K_m. Doubt is cast on the suitability of formic acid as a solvent for polyvinyl alcohol in viscosity determinations by Hermann's finding (U.S.P. 2 278 783) that esterification of the alcohol occurs readily therein at room temperature and in the absence of a catalyst. Water itself does not appear to be a perfect solvent for polyvinyl alcohol: in the cold, a clear solution is not always obtained, heat being sometimes necessary to disperse the substance completely. Marked differences in viscosity of polymeric substances have been observed in " good " and " poor " solvents (Kemp and Peters, *Ind. Eng. Chem.*, 1942, **34**, 1192). For these reasons the validity of molecular-weight determinations of polyvinyl alcohol by the viscosity method are open to considerable doubt.

However, the viscosity method adequately served the purpose of the present investigation which was to compare the chain lengths of polyvinyl acetate samples before and after treatment and retreatment and, similarly, of polyvinyl alcohol samples derived from the foregoing esters. To conform with McDowell and Kenyon's data the Staudinger relationship, despite its inaccuracy, has been applied and for convenience the same value for K_m has been adopted for both polyvinyl alcohol and polyvinyl acetate. The molecular-weight and chain-length values quoted have no absolute significance but they serve to reflect changes.

Specific-viscosity determinations were carried out in B.S.S. Ostwald-type viscometers at 25° ± 0·02°. Molecular weights and average degrees of polymerisation were derived from the Staudinger relationship $M = \eta_{sp.}/CK_m$, with a value of $2{\cdot}6 \times 10^{-4}$ for K_m. Throughout, acetone was used as the solvent for the acetates and water for the alcohols and the concentration was of the order of 0·10 g. in 100 ml. of solution. All samples were dried at 105° for 1 hour under vacuum before weighing. Viscosity measurements were carried out in duplicate and the mean values used. The calculated values of the average degree of polymerisation (D.P.) and molecular weight (M) are presented in Table 1.

TABLE 1.

	I. Original polyvinyl acetate		Ia. Polyvinyl alcohol by hydrolysis of I		II. Polyvinyl acetate by re-acetylation of Ia		IIa. Polyvinyl alcohol by hydrolysis of II		III. Polyvinyl acetate by re-acetylation of IIa	
Grade	D.P.	*M*	D.P.	*M*	D.P.	*M*	D.P.	*M*	D.P.	*M*
Gelva 7	145	12 450	184	8 100	147	12 600	165	7 260	151	13 000
Gelva 15	205	17 700	205	9 000	178	15 300	209	9 200	177	15 200
Gelva 45	373	32 000	305	13 400	250	21 500	297	13 100	254	21 850

The molecular weight of the polyvinyl alcohol obtained from Gelva 15 by hydrolysis according to Staudinger, Frey, and Starck's method with methyl alcoholic sodium methoxide was also determined: Average D.P. of first preparation, 253; M, 11 100; average D.P. of second preparation, 245; M, 10 800.

The cycle starting with the commercial polyvinyl alcohol RH.349 gave the following results:

I. Polyvinyl alcohol, RH. 349		II. Polyvinyl acetate from I		III. Polyvinyl alcohol from II	
D.P.	*M*	D.P.	*M*	D.P.	*M*
344	15 100	295	25 400	293	12 900

Stability of Solutions of Polyvinyl Acetate in Technical Mustard Gas.—The viscosities of solutions of the original and reacetylated polymers in mustard gas were investigated at 25°, 60°, and 100° in the viscometer shown in Fig. 1. Owing to the difficulty of introducing a constant volume of viscous liquid the original viscosity of the mustard gas solution was determined first in either a No. 3 or a No. 4 B.S.S. Ostwald-type viscometer with the standard attachment for closing the top of the U-tubes and for raising the liquid into the upper bulb. The small bulbs normally packed with cotton wool were filled with granulated active carbon. The No. 4 viscometer was calibrated with castor oil of known viscosity as determined in a No. 3 viscometer standardised with 60% sucrose solution. The viscosity of the freshly prepared mustard gas solutions having been determined, the solutions were introduced into the modified viscometer through the side-arm *A* without wetting the sides of the glass. The side arm was then sealed off. The lower bulb *B* was filled until the level of the liquid was just below the point of entry of the side-arm *C*. The diameter and length of the capillary and the dimensions of the viscometer were such as to correspond roughly to a No. 3 or No. 4 B.S.S. viscometer according to the viscosity range to be covered. For an observation the instrument was inverted so that the contents of the lower bulb *B* ran through the wide side-arm *C* and filled the bulbs *D* and *E* giving a continuous thread of liquid in the capillary. When the viscometer was returned to the normal position the excess of liquid ran back through *C* and the contents of *D* and *E* passed through the capillary. The meniscus was timed from mark 1 to mark 2 and in this manner determinations were repeated as often as desired, without opening the apparatus and without fear of contamination. Bulb *D* served to give the operator more time in which to make the necessary adjustments to the vertical and allowed the excess of viscous fluid in *C* to return to *B*. To avoid drainage errors the side-arm *C* was joined to bulb *D* at an acute angle. A most important constructional feature was the length of the tube leading from the capillary to the liquid in bulb *B*: this must be such that when the viscometer is inverted and the liquid has come to rest no part of the tube should extend above the liquid level, otherwise when the instrument is returned to the normal position an air bubble is trapped in the tube and passes into the capillary. Further, when in the normal position, the end of the tube must be below the liquid level so as to ensure even flow through the capillary.

All viscosity determinations were carried out at 25° ± 0·02°. The mustard gas solutions were stored in the sealed modified viscometers at 100° ± 0·25°, 60° ± 0·25°, or 25° + 0·2°; those at the higher temperatures were removed at intervals, inverted, allowed to cool at room temperature for ½ hour and thereafter for sufficient time to attain the temperature of the 25° thermostat before measurement of the viscosity. In the storage baths the whole of the viscometer was submerged while a ball-and-socket fitting permitted easy inversion and adjustment to the vertical in the 25° thermostat.

The mustard gas solutions of the acetates were prepared at room temperature by stirring the pulverised resin with the mustard gas in a round-bottomed flask fitted with a glycerol-vapour seal. Complete dissolution was effected in about 18 hours. The polymer solutions were filtered and used directly for density and viscosity measurements in the B.S.S. viscometers. Part of the same solutions was introduced into the modified viscometers which were then sealed. From the time of flow in this instrument at 25° the constant of the viscometer was calculated; this was then used in all subsequent viscosity determinations. The viscosity–time of storage data for Gelva 15 (13% solution), reacetylated Gelva 15 (10% solution), and reacetylated Gelva 45 (10% solution) at 25°, 60°, and 100° are presented in Figs. 2, 3, and 4 respectively.

The polymer solutions darkened very considerably on storage at the three temperatures. It is also clear from the results that taking the polyvinyl acetate through the cycle acetate ⟶ alcohol ⟶ acetate produces a marked effect as shown by the different forms of the viscosity–time of storage curves for the original and reacetylated materials. There is no certainty that the use of the highest temperature (100°) served to accelerate the changes taking place at lower temperatures, 25° and 60°—other reactions may have complicated the issue. At 100° the viscosity of the Gelva 15, reacetylated Gelva 15, and reacetylated Gelva 45 solutions increased rapidly and progressively and in a comparatively short time gel formation ensued. With the reacetylated Gelva 45 gel formation was more rapid than with either of the Gelvas 15. It is possible that had the first reading been taken after a shorter time the early portion of the curve might have been different: an initial phase of viscosity reduction similar to that observed at the lower temperatures might have been missed on this account.

The results of the storage tests at 60° revealed some interesting differences between original and reacetylated polyvinyl acetates. At this temperature the mustard gas solution of Gelva 15 showed a progressive decrease in viscosity during 106 days covered by the experiments, during

which time the viscosity was reduced by almost a half. In marked contrast a solution of the corresponding reacetylated material showed only an initial and very slight depression in viscosity followed by a steady increase for a long period, but in the later stages there appeared a tendency for the viscosity to fall off again. Similarly, in the concluding stages of the tests on reacetylated Gelva 45 a falling-off in viscosity was also observed. The incidence of this phase marked by departure from the rising part of the curve coincided with the first observation of the deposition from solution in progressively increasing amount of some insoluble finely divided material.

At 25° the viscosity changes during the period of test were small but the trend was the same as at 60°. The interesting point was that whereas the original polymer solution progressively decreased in viscosity the reacetylated polymer solutions showed only a slight initial reduction in viscosity, the curve passed through a minimum, and then continued to rise steadily.

The factors responsible for the initial downward trend of the viscosity–time of storage curves having been elucidated to some degree, an attempt was made to find out the underlying cause of the subsequent increase in viscosity. Solutions of polyvinyl acetate (Gelva 15 and 45) in the same grade of technical mustard gas which had been stored at 60° in varnished-metal containers for 17 weeks were examined. The first was a solution of Gelva 15 of original viscosity 12·3 poises at 10°. After 17 weeks' storage the viscosity had been reduced to 5·2 poises. The second was a solution of Gelva 45 of original viscosity 11·65 poises at 10°; its viscosity had been reduced to 2·05 poises during the same period. Both solutions were very dark and contained an appreciable amount of sediment; this was removed by filtration and was not examined further. Viscosity determinations at 25° on the filtrates gave the following results: Gelva 15 solution, 2·90 poises; Gelva 45 solution, 1·43 poises. Samples of the polymers were recovered from the solutions by precipitation in a large volume of ether. This gave dark brown rubbery masses, which were washed with fresh volumes of ether and then heated with a large volume of water on the steam-bath. This hot-water treatment was repeated several times with fresh quantities of distilled water until all the occluded mustard gas had been hydrolysed and removed. The materials were then dried in a vacuum at 105°. When dry they were dark brown brittle resins, completely insoluble in all the usual solvents for polyvinyl acetate showing a marked tendency to swell to soft rubber-like masses. Owing to this insolubility no estimate of their molecular weights could be made. The materials had all the properties of highly cross-linked derivatives. Both contained sulphur and chlorine (Found, for recovered Gelva 15 and 45 respectively: Ac, 38·0, 32·7; Cl, 1·85, 2·55; S, 1·85, 2·6%). On hydrolysis the recovered polymers did not give water-soluble derivatives.

Constitutional changes in the polymer during storage in the mustard gas solution were also investigated. The bulk of the Gelva 15 solution made up for the viscosity determinations was introduced by suction into a flask which was immersed in the 60° thermostat. A sample of the polymer was recovered from this solution before the commencement of the storage tests. At intervals, some of the polymer solution was withdrawn by siphoning for examination of the polymer. The procedure already outlined, *viz.*, precipitation with ether, and repeated washing with hot water, was adopted for working-up the recovered polymer. The sample of polymer recovered from the mustard gas solution directly it had been made up, *i.e.*, before storage at 60°, had already suffered some slight change. There had been a noticeable darkening; it contained traces of chlorine but no sulphur. Hydrolysis showed only 45·5% of acetyl, against 50% for the original Gelva 15; boiling with N-alkali for this determination revealed a very small amount of brownish solid remaining undissolved. Under the same conditions polyvinyl acetate is completely hydrolysed to water-soluble polyvinyl alcohol. The material was not completely soluble in acetone, an exceedingly small fraction remained undissolved; this was filtered off; the average D.P. calculated from the specific viscosity was 211 compared with 205 for the original Gelva 15.

The polymer recovered after 7 days' storage at 60° showed even greater modification. It was darker and contained traces of both chlorine and sulphur. The acetyl content had been reduced to 46·7%. The material contained a higher proportion of alkali- and acetone-insoluble material. No specific-viscosity determination was carried out on this specimen for this reason. Instead, a portion of the material was exhaustively extracted with acetone in a Soxhlet apparatus and the soluble and the insoluble fraction were isolated separately. This procedure was followed in the examination of all subsequent samples of recovered polymer. Sulphur, chlorine, and acetyl determinations were carried out on both soluble and insoluble fractions and, in the case of the former, specific viscosity determinations in acetone solution (a value of $2{\cdot}6 \times 10^{-4}$ was assigned to K_m). The results are summarised in the following table.

TABLE 2. *Changes in composition of Gelva* 15 *stored in mustard gas solution at* 60°.

Soluble fraction.

Time of storage (days)	Acetone-soluble, %	D.P.	Ac, % *	S, % *	Cl, % *
0	~100	211	48·5	Nil	Trace
7	<100	310	42·4	0·37	0·71
16	82·9	300	43·7	0·07	0·83
28	47·5	176	47·0	0·69	0·67
54	76·7	229	41·7	1·27	0·83
83	62·6	169	54·7	1·13	1·24

Insoluble fraction.

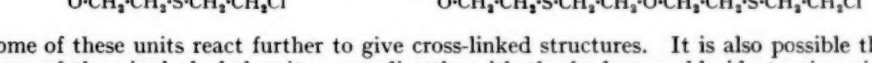
Time of storage (days)	Acetone-insoluble, %	Ac, % *	S, % *	Cl, % *
7	—	54·6	0·45	1·05
16	16·6	42·9	0·26	1·60
28	52·0	51·1	0·08	0·63
54	24·2	44·5	0·63	1·18
83	38·0	43·9	0·92	1·23

* Microanalyses by Drs. Weiler and Strauss, Oxford.

The values quoted for acetyl content are based on the assumption that it was the only hydrolysable group present. It is highly probable that some hydrogen chloride was also removed in some cases and these results are therefore of doubtful value. Little reliance can also be placed on the values for the average degree of polymerisation of the acetone-soluble portions of the recovered polymer.

DISCUSSION

The interpretation of these results is complicated by the fact that the mustard gas used was a technical mixture of two compounds. In both compounds the main reactivity resides in the ω-chlorine atoms and in general their reactions are very similar. The reduction of acetyl content of the recovered polymer, the presence in the polymer of both sulphur and chlorine, and the peculiar solubility relations in acetone point to reaction between polymer and solvent leading to a cross-linked structure. Polyvinyl alcohol is known to form cross-linked derivatives with terminally substituted dichloro-compounds such as glycerol, 1 : 3-dichlorohydrin, dichlorodimethyl and dichlorodiethyl ether (Jones, *Brit. Plastics*, 1944, **16**, 81) and presumably mustard gas will react similarly. It seems likely that some of the acetate groups in the polyvinyl acetate have undergone hydrolysis under the catalytic influence of hydrogen chloride from the mustard gas mixture. The vinyl alcohol units thus introduced into the chain are then attacked by mustard gas to give



Some of these units react further to give cross-linked structures. It is also possible that some of the vinyl alcohol units react directly with the hydrogen chloride to give vinyl chloride units. The existence of cross-bonds would explain the insolubility of the recovered polymer and its marked swelling under the influence of solvents. All these reactions are dependent on the presence of water in the system : considerable support for this theory of the reaction mechanism is forthcoming from the work of Morrison, Mungen, *et al.* (unpublished Canadian Reports, Ministry of Supply) who showed that gelation does not appear in pure mustard gas or in technical mustard gas to which 5% of acetic anhydride has been added.

The observed viscosity changes on storage are clearly the net result of two opposing tendencies—a chain-breaking mechanism and a cross-linking process, the former predominating in the early stages. It appears from Table 1 that in the case of Gelva 7, the polymer of lowest molecular weight, there is no change in average degree of polymerisation when the acetate groups are removed by alkaline hydrolysis and subsequently restored by acetylation. However, with the polymers of higher molecular weight, Gelva 15 and Gelva 45, there is a definite reduction in chain length in this cycle of operations and the higher the molecular weight the greater the reduction. Reduction below 50% has never been

observed. All the reacetylated polymers suffer no further change when subjected a second time to hydrolysis and reacetylation. The good agreement between the degree of polymerisation values for polyvinyl alcohols I*a* and II*a* suggests that chain rupture takes place during the original hydrolysis and not during reacetylation.

The results for the commercial polyvinyl alcohol RH.349 (Table 2) appear somewhat anomalous in that degradation seems to have occurred in the reacetylation stage. It may be significant that the acetylation reaction here appeared to be more difficult to complete. The reacetylated material contained only 48·74% of acetyl, against 50% for complete esterification. (The author has no information about the method of hydrolysis used in the commercial preparation of RH.349.) The value for the average degree of polymerisation of the polyvinyl alcohol obtained from Gelva 15 by methyl-alcoholic sodium methoxide is appreciably higher than the value quoted in Table 1; this suggests that the amount of degradation varies with the method of hydrolysis.

All the evidence points to the occurrence in polyvinyl acetate of high molecular weight of some weak links which are vulnerable under the conditions of alkaline hydrolysis. Reference has been made to the suggestion that these may be oxygen bonds. It is of interest that Kornblum and De La Mare (*J. Amer. Chem. Soc.*, 1951, **73**, 880) recently demonstrated the ready decomposition of *tert.*-butyl 1-phenylethyl peroxide by bases such as potassium hydroxide, sodium ethoxide, or piperidine. The mechanism advanced to explain this decomposition presupposes the existence of a hydrogen atom on the carbon attached to the peroxide linkage and consequently only those dialkyl peroxides where this condition is fulfilled will undergo this base-catalysed decomposition. A peroxide linkage in polyvinyl acetate might conceivably be ruptured in this manner on alkaline hydrolysis and so would yield a polyvinyl alcohol with a terminal aldehydic group. Further evidence is clearly needed before the true nature of these weak linkages in polyvinyl acetate can be truly established.*

Figs. 2 and 3 reveal a striking difference in behaviour between parent polyvinyl acetate and the same polymer after alkaline hydrolysis and acetylation. The first phase of viscosity reduction is much less evident in the latter but it is significant that it has not altogether disappeared. It would therefore seem that some of the weak bonds have survived the mild hydrolytic treatment but these are ruptured on contact with the mustard gas mixture.

This work was carried out for the Ministry of Supply in 1944 and grateful acknowledgment is made to the Chief Scientist, Ministry of Supply, and to the Director of the Chemical Research Laboratory for permission to publish. The author is also indebted to Professor H. W. Melville, F.R.S., for his interest and stimulating advice during the course of the work and to Mr. W. Kynaston for assistance with the viscosity determinations.

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* Wheeler, Ernst, Kennedy, and Crozier (Amer. Chem. Soc. Spring 1951 Meeting, Abstracts) have recently presented evidence indicating that the reduction in molecular weight of polyvinyl acetate on hydrolysis and reacetylation is due to the removal of polymer branches attached to the parent polymer through acetate groups. It is suggested that these side branches result from transfer reactions with the C–H bonds of the acetate groups of both monomer and polymer. Other vinyl esters are shown to undergo a similar degradation. Also it is shown that polyvinyl alcohol molecules can unite with each other under certain conditions and hence mask this degradation.

161. *Losses of (Radioactive) Sulphur and Phosphorus from Resting Bacterial Cells.*

By T. C. N. Carroll, C. J. Danby, A. C. R. Dean, and Sir Cyril Hinshelwood.

By the use of the radio-isotopes ^{35}S and ^{32}P it has been shown that there is a gradual loss of sulphur and phosphorus from cells of *Bact. lactis aerogenes* which are suspended in a synthetic medium containing all growth requisites except a source of carbon. Such losses occur predominantly while the cells are still alive, and are slowed down abruptly if the cells are killed. Subsequent lysis is (at pH 7) a very much slower process.

No simultaneous uptake of sulphate or phosphate from the medium has been detected under these conditions. The implications of these findings are considered : a lively exchange within the still living cell is suggested, whereby internal concentrations are maintained and feed the slow irreversible outflow.

Considerable interest attaches to the question of the chemical activities of non-growing cells, which are much greater than is implied by the term resting. In particular, it was desired to study material exchanges occurring during the slow decline of a population of *Bact. lactis aerogenes*, since information on this matter is of importance in connexion with the law governing the death-rate (cf. *Nature*, 1951, **167**, 666).

The application of radio-isotopes according to the well-known principles (cf. *Cold Spring Harbor Symp. Quant. Biol.*, 1948, **13**; especially Hevesy, p. 129) was the obvious method of obtaining the required information.

This work has been carried out on suspensions of *Bact. lactis aerogenes* in a synthetic medium containing ammonium and magnesium chlorides, ammonium sulphate, potassium phosphate, and a buffer of either phosphate or phthalate.

Owing to the absence of a source of carbon no growth can take place in such a medium and the cells are said to be in the " non-proliferating " state. According to the temperature, the life of such cells may range from a few minutes to several months, and the object is to discover what changes occur in the sulphur and phosphorus contents during the gradual decline of the viable population.

Loss of Sulphur from " Non-proliferating " Cells.—Bacteria grown on a medium containing sulphate labelled with ^{35}S were suspended in a medium buffered with phosphate (pH 7), and placed in a thermostat. Samples were removed at intervals and the bacteria separated in a centrifuge so that the activity of the clear supernatant medium could be determined with a Geiger counter. The viable count of the suspension was estimated at suitable times by the usual plating technique.

Experiments at both 40° and 25° were conducted. At the latter temperature two parallel runs were made, one with a high concentration of inactive sulphate in the medium, the other with only about the same total amount as in the bacteria themselves.

The results are shown in Fig. 1, where the activity of the supernatant medium represents sulphur lost from the cells.

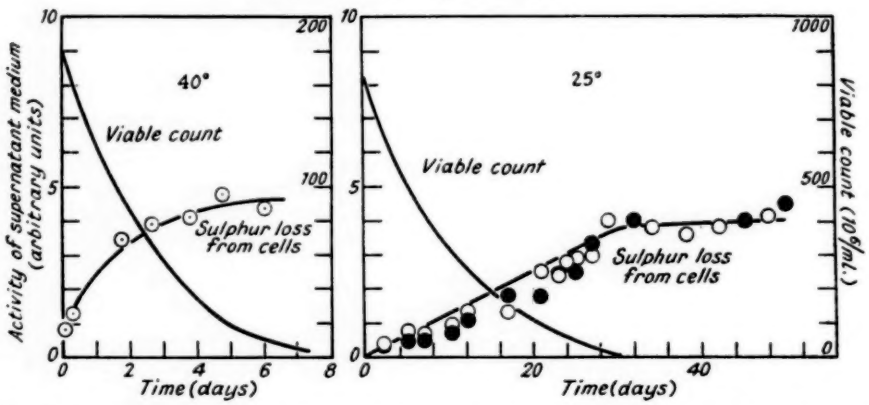
Loss of Phosphorus from " Non-proliferating " Cells.—In order that the phosphate concentration might be varied as desired without effect on the buffering capacity of the medium, a phthalate buffer (pH 6·5) was employed for these experiments, which were made on suspensions of bacteria grown in phosphate labelled with ^{32}P. The difference in pH between a phthalate and a phosphate buffer is in fact insufficient to produce a significant difference in the death rate of *Bact. lactis aerogenes*. At a given temperature, therefore, the results of the respective experiments with sulphur and phosphorus are quite comparable. This was confirmed by the results of an experiment with a culture that had been grown in a medium containing active sulphate and active phosphate together.

The results are shown in Fig. 2.

Effect of killing the Bacteria on the Sulphur and Phosphorus Losses.—A suspension of radioactive cells was prepared as in earlier experiments. After a few hours at 40° two large

portions were removed. In one the cells were killed by the addition of formaldehyde and in the other by heating them to 70° for five minutes. Each sample was then replaced in the 40° thermostat, and samples were removed at intervals for determination of the activity of the medium, which, as before, would indicate the loss of sulphur or phosphorus from the cells.

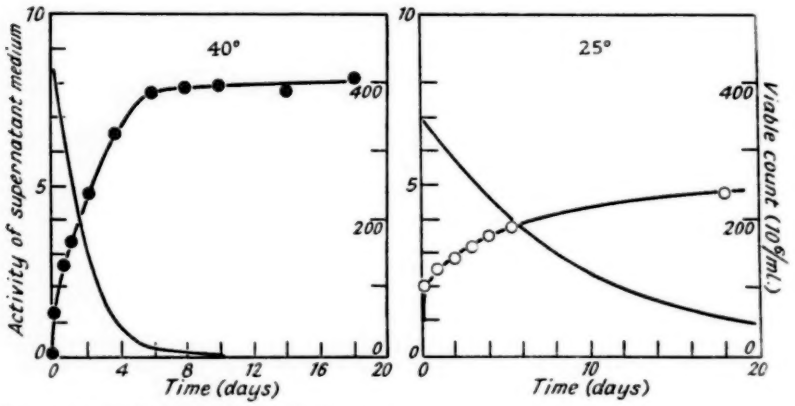
FIG. 1. *Loss of ^{35}S from resting cells.*



Rising curves give activity of supernatant liquid in arbitrary units so chosen that total activity of whole suspension = 10 (left-hand scales).

Falling curves give viable counts (right-hand scales). In right-hand diagram, ● 1·82 g. of SO_4'' per l. of medium; ○ $2{\cdot}6 \times 10^{-3}$ g./l.

FIG. 2. *Loss of ^{32}P from resting cells.*



Falling curves (right-hand scales), viable count.

Rising curves (left-hand scales), activity of supernatant liquid, *i.e.*, loss of phosphorus from cells.

The results are shown in Fig. 3 and Fig. 4.

Uptake of Sulphur and Phosphorus from the Medium.—For these experiments the bacteria were grown on inactive sulphate and phosphate.

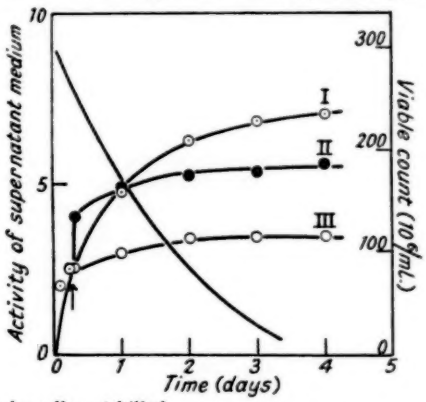
For the study of phosphorus uptake the suspending medium was buffered with phthalate and contained a known amount of labelled phosphate, while for the study of sulphur uptake the medium contained a known amount of labelled sulphate and was buffered with phosphate.

In order that a small uptake by the cells might be detected, the labelled sulphate or phosphate added to the medium was of very small amount but of high specific activity.

In each suspension initially the total amount of labelled element (active plus inactive) in the medium was approximately equal to that in the cells themselves (inactive). In order to fulfil this condition one litre of a suspension containing, for example, 200 million/ml. would require only 2·5 mg. of sulphate ion or 20 mg. of phosphate ion in the medium.

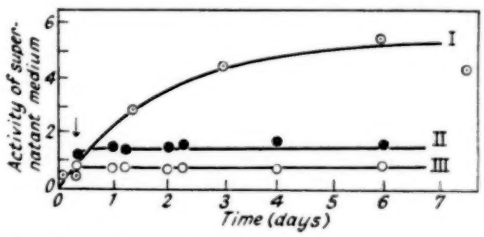
In the conditions of the experiments no significant uptake of the active elements could be detected.

FIG. 3. *Loss of* ^{32}P *(at 40°) from cells killed by heat or formaldehyde.*



I, Control—cells not killed.
II, Killed by heat after 6·5 hours (indicated by arrow).
III, Killed by formaldehyde after 6·5 hours (indicated by arrow).
Activity of whole suspension = 10 units.

FIG. 4. *Loss of* ^{35}S *(at 40°) from cells killed by heat or formaldehyde.*



I, Control—cells not killed.
II, Killed by heat after 8 hours (indicated by arrow).
III, Killed by formaldehyde after 8 hours (indicated by arrow).
Activity of whole suspension = 10 units.

DISCUSSION OF RESULTS

When cells of *Bact. lactis aerogenes* are suspended in a synthetic medium containing all growth requirements except a source of carbon the number of viable cells per ml. (viable count) decreases with time, the death rate depending on the temperature of the suspension. At 40° in the conditions of these experiments it is such that after 7 days the viable count falls to less than one-tenth of its initial value, while at 25° a corresponding fall occurs in about 30 days.

At both these temperatures cells labelled with ^{35}S are found to lose their activity to the surrounding medium at a rate which decreases in much the same way as the viable count itself (Fig. 1). The rate at which the ^{35}S appears in the medium as a consequence of this loss is independent of the concentration of inactive sulphate outside the cell.

As can be seen from Fig. 2 the behaviour of phosphorus is very similar in that the rate of loss of ^{32}P from the cells to the medium falls off approximately in parallel with the viable count itself. The main difference is that the cell can lose phosphorus much more

extensively than sulphur, so that by the time the viable count becomes negligible at least 80% of the total phosphorus has been lost, but only 40% of the total sulphur. This result is perhaps hardly surprising since a considerable part of the cell phosphorus may be present as phosphate esters while the sulphur is probably present mainly as protein.

The experiments in which the cells were deliberately killed were designed to answer the question whether the loss of sulphur and phosphorus from bacteria is due to an activity of the viable cell, or rather to a rapid autolysis of the cell after death. In either case the rate of loss would run parallel with the viable count as is actually found. If, however, the cells are killed soon after suspension, then a clear-cut answer can be obtained.

The experiments made with ^{35}S and with ^{32}P respectively (Figs. 3 and 4) show conclusively that it is the viable cells which are principally responsible for the loss of sulphur and phosphorus to the medium. In each case there is an appreciable loss from the cells during the actual process of killing by heat, and this is almost certainly due to the increase in metabolic activity of the cells as the temperature is raised. After this, however, the rate of loss falls to quite small values. It is interesting to note in the case of phosphorus that even after the killing the loss continues though at a much diminished rate for approximately 36 hours, whence it appears that the partially degraded phosphate esters presumably present in the cell at the moment of death can continue to escape by a purely non-biological process. The absence of such a phenomenon with the sulphur suggests that under these conditions the protein breakdown can be accomplished readily only by the living cell.

The next question is whether or not these losses from the viable cell are accompanied by a simultaneous uptake of sulphate and phosphate from the medium. This is answered by the experiments on the suspension of non-radioactive bacteria in the synthetic medium containing radioactive sulphate or phosphate, the conditions being so arranged that initially there is approximately the same amount of either element in the cells as in the medium.

Neither with sulphur nor with phosphorus is any uptake indicated, though the counting techniques employed would detect an uptake of 5—10% of the labelled component. Any uptake, therefore, is insufficient to offset more than a small fraction of the simultaneous loss from the cell. Once the great majority of cells are dead, survivors may well use lysed cell material as a source of carbon and maintain a steady turnover of essential elements with little overall loss, and though such systems might yield results of interest they are outside the scope of the present discussion.

As to the general implication of these various results, it might perhaps have been expected that one of two types of behaviour would be observed: (*a*) an irreversible loss of material from dead and lysing cells, or (*b*) a more or less lively exchange between living cells and the surrounding medium. In fact, while there is predominantly a loss, it is one which occurs from still living cells.

The simplest interpretation of this finding is as follows. There is an active internal exchange of material between various parts of the living cell. The bacterial mechanism is still largely organised for syntheses so that breakdown products from one part are to some considerable extent salved and used for re-synthesis of other parts. The salvage is, however, imperfect and is accompanied by a steady leakage from the cell. There is little or no corresponding uptake from the medium since the internal concentrations maintained by the exchange within a cell exceed the relevant external concentrations.

The significance of processes of this kind in connexion with the law governing the death rate of bacteria has recently been discussed (*Nature*, 1951, **167**, 666) and the theory put forward that internal exhanges of material play an important part in determining the form of this law. The present results appear to provide further evidence that the slow process of cell decline is indeed superposed on a vigorous internal activity.

Experimental

Materials.—Organism. A strain of *Bact. lactis aerogenes* was used and was maintained by daily serial subculture in a standard synthetic medium.

Synthetic media. (1) *Standard synthetic medium.* This was prepared by mixing under aseptic conditions sterile solutions of glucose (50 g./l.), phosphate buffer (2·96 g. of KH_2PO_4 +

16·0 g. of $Na_2HPO_4,12H_2O$/l.), ammonium sulphate (5 g./l.), and magnesium sulphate (1 g./l.) in the ratios 10 : 10 : 5 : 1.

(2) *Sulphur-free medium.* The ammonium and magnesium sulphates in the standard synthetic medium were replaced by equivalent amounts of ammonium and magnesium chlorides.

(3) *Phosphorus-free medium.* The phosphate buffer of pH 7·1 in the standard synthetic medium was replaced by an M/15-potassium hydrogen phthalate buffer of pH 6·5.

Preparation of Suspensions.—Bacteria containing ^{35}S. The strain of *Bact. lactis aerogenes* in the standard synthetic medium was inoculated into the sulphur-free medium and was serially subcultured in it several times until the bacterial count was limited by the sulphur present as impurity in the medium. 0·1 Ml. of the latter culture was then inoculated into 100 ml. of the sulphur-free medium and, when growth had ceased after the assimilation of all the sulphur present as impurity (a bacterial count of about 20×10^6 per ml. was usually reached), 1·0 mc of carrier-free $^{35}SO_4''$ in phosphate buffer at pH 7·12 was added. When growth had again ceased sufficient inactive sulphate was added to bring the bacterial count to the desired value. In these experiments the specific activity of the $^{35}SO_4''$ was such that 1·0 mc corresponded to the support of a population of about 8×10^9 bacteria, which was usually about one-half of the total bacterial mass required. The bacteria from the fully grown culture were then separated in a centrifuge, and the cells were washed three times with phosphate buffer and then re-suspended in a medium containing phosphate buffer, ammonium chloride, and magnesium chloride in the ratios 10 : 5 : 1 together with the requisite amount of inactive sulphate.

Bacteria containing ^{32}P. A suspension of bacteria in the standard synthetic medium was inoculated into 26 ml. of phosphorus-free medium to which had been added enough inactive phosphate to give a bacterial count of 10^9 per ml. After several subcultures in this medium a small inoculum (0·02 ml.) was transferred to 260 ml. of phosphorus-free medium containing 0·5 mc of $^{32}PO_4'''$ and enough inactive phosphate to support a bacterial count of 230×10^6 per ml. The cells were separated in the usual manner, washed three times with phthalate buffer, and re-suspended in a medium containing phthalate buffer, ammonium sulphate, and magnesium sulphate in the ratio 10 : 5 : 1 and the desired amount of inactive phosphate.

Uptake of ^{35}S.—A culture of bacteria in the standard synthetic medium was centrifuged. The cells were washed three times with phosphate buffer and re-suspended in a medium containing phosphate buffer, ammonium chloride, and magnesium chloride in the ratios 10 : 5 : 1 together with carrier-free $^{35}SO_4''$.

Uptake of ^{32}P.—The method was similar to that for the experiments on the uptake of ^{35}S except that the cells were washed with phthalate buffer and were re-suspended in a medium containing this same buffer, ammonium sulphate, and magnesium sulphate in the ratios 10 : 5 : 1, and the necessary $^{32}PO_4'''$.

Measurement of Radioactivity.—A separate appendix on counting techniques is given.

Appendix

The determination of radioactive sulphur in experiments with bacterial suspensions

In tracer experiments the measurements of activity are usually made either on solid or on liquid samples by the use of the appropriate type of Geiger counter. Liquid samples are particularly convenient and usually require little preparation, but as the minimum wall thickness of conventional counter-tubes for liquids corresponds to about 25 mg./cm.^{2} these cannot be used with tracers which emit only low-energy β-radiation. ^{35}S has consequently been determined almost exclusively in solid samples, with the use of thin end-window counters or of counters in which the sample is placed inside the tube itself (Hendricks, Bryner, Thomas, and Ivie, *J. Phys. Chem.*, 1943, **47**, 469). With low-energy β-emitters large corrections for self-absorption of the radiation become necessary and considerable errors can arise from small irregularities in the solid samples. This is particularly evident in work with small specific activities which necessitates relatively thick samples. Comparison of different solid samples is inaccurate unless the self-absorption correction is the same for all, *i.e.*, unless they are in the same chemical form. With sulphur, quantitative conversion into sulphate is usually necessary—a process which is frequently difficult.

In the present work it has been found possible to measure ^{35}S in liquid samples by the use of a conventional thin-window counter placed very close to the upper surface of an extended area of the liquid. Errors due to uncertainties in the self-absorption corrections are eliminated as all samples in the same solvent are of substantially the same density and of virtually

infinite thickness for the radiation from ^{35}S (greater than 0·3 mm. of water). The chemical nature of the dissolved substance is not significant (unless adsorptive phenomena take place, as discussed below).

Experimental

The liquid samples were mounted on glass plates on which they were confined by a wax ring about 6 cm. in diameter, deposited from a solvent. By a screw mechanism and an optical system the samples were raised till their upper surfaces were a standard small distance from the window of the counter (mica, 2 mg./cm.^{2}; counter, type EHM 2). The electronic counting equipment was of the conventional kind, and the corrections applied to the observed rates of count were as described previously (Carroll, Danby, Eddy, and Hinshelwood, *J.*, 1950, 946).

Sources of Error, especially Those due to Adsorption.—Preliminary experiments with solutions of inorganic ^{35}S compounds showed that the liquid-counting technique was satisfactory provided

Fig. 5. Fig. 6.

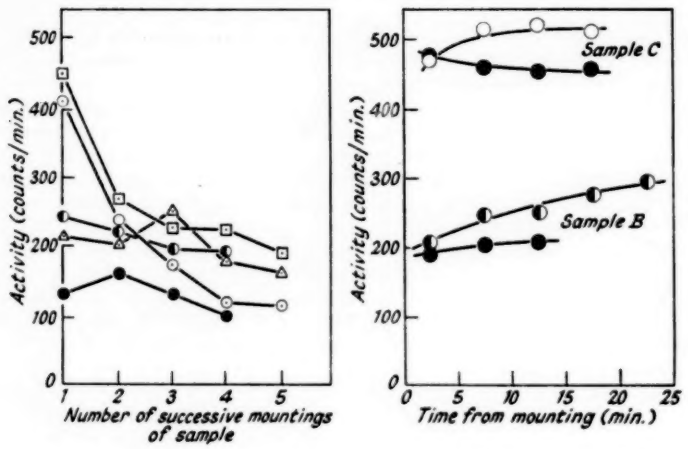


Fig. 5. *Effect of successive remounting of sample on observed activity.*

Sample *A*, treated with: ○ methionine, cysteine, and sulphite; ⊡ with sulphite; △ with bacterial lysate.

Sample *B*, treated with: ◐ alkaline sulphide; ● bromine water.

Fig. 6. *Variation in observed activity with time after mounting.*

○ Sample untreated.
◐ Treated with alkaline sulphide.
● Treated with bromine water and sulphate.

that sufficient inactive carrier was present to eliminate the effects of adsorption. In the bacterial work, however, the concentrations of sulphur compounds were very small (about 10^{-8} g./10^9 cells). This necessitated the use of ^{35}S of high specific activity, and adsorption on glassware, particularly on the plates on which the samples were mounted, became important. Adsorption at the air–liquid interface can also take place and lead to a higher concentration of the active material at the surface; with a weak β-emitter this leads to too high an apparent activity, as determined by a counter placed above the surface (Salley, Weith, Argyle, and Dixon, *Proc. Roy. Soc.*, 1950, *A*, **203**, 42). With a bacterial suspension containing ^{35}S the sedimentation of cells away from the surface can lead to a progressive decrease in the rate of count recorded.

Experiments on these effects are described below.

(1) *Adsorption on glass.* In Fig. 5 is shown the progressive decrease in activity observed when a typical sample of the solutions used in the work already described is successively remounted on a series of clean glass plates. This fall is probably due largely to adsorption of the sulphur-containing substance on the glass. The influence of a number of added sulphur compounds in reducing the loss was therefore studied. Methionine, cysteine, and sulphate ions show

little effect. Sulphite, sulphide, and a solution containing lysed bacteria reduce the loss in activity. A water-repellent silicone film coating all glassware greatly reduces adsorption and leads to more reproducible results, but when this is used on the mounting plates a more effective barrier than a wax ring is required to contain the samples.

(2) *Adsorption at the air–liquid interface.* Sulphur which leaves bacterial cells seems to be in a reduced state and may be partly in combination with various long-chain protein residues as surface-active compounds. Their concentration at the surface would explain the high initial rates of count observed with several of the samples illustrated in Fig. 5. Added sulphide and bacterial lysate both appear to reduce the effect of this adsorption, probably by undergoing exchange with the active sulphur in the surface film and so distributing it more uniformly through the liquid. Oxidation of sulphur to sulphate with bromine water and addition of inactive sulphate to counteract the effect of adsorption on the glass proved to be the most effective treatment. Fig. 6 shows the variation in the observed rate of count during the first 15—20 minutes after the placing of the samples on the mounting plates. Where the concentration of active material in the surface layers is not prevented there is a progressive slow increase in activity. In contrast, the samples treated with bromine show little change in observed rate of count. A drop of wetting agent added to one of the latter samples reduced the counting rate to half its previous value: here the surface layer contains no active sulphur and acts as a barrier to the escape of radiation from the liquid below (Judson, Argyle, Salley, and Dixon, *J. Chem. Phys.*, 1950, **18**, 1302).

(3) *Sedimentation of bacterial cells.* The activity contained in the cells of a culture grown in the presence of radioactive tracer can be determined in two ways: either from the difference in the activity of the whole suspension and that of the clear medium from which the cells have been removed by centrifuge, or by direct measurement on the sludge of bacteria obtained by centrifugation, allowance being made for the activity of the liquid remaining in it (Carroll *et al.*, *loc. cit.*). With ^{35}S the activity of the whole suspension cannot be determined accurately owing to the sedimentation of the cells away from the surface which leads to a progressive decrease in the rate of count. This difficulty is avoided by destruction of the cells with a little concentrated sulphuric acid, followed by oxidation of the bacterial sulphur to sulphate by bromine. By a similar treatment it is possible to measure the activity of the centrifuged bacterial sludge.

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162. *The Absorption Spectrum of Allene in the Vacuum Ultra-violet.*

By L. H. SUTCLIFFE and A. D. WALSH.

The absorption spectrum of allene has been photographed in the vacuum ultra-violet. Most of the bands to short wave-lengths of 1800 Å can be classified as separate electronic transitions belonging to numerous Rydberg series. Some of these series are only fragmentary, but all appear to converge to the same ionization limit, 10·19 ± 0·01 v. Some discussion of the nature of the series is given. Continuous absorption to long wave-lengths of 1800 Å probably represents several different non-Rydberg transitions.

PRICE, TEEGAN, and WALSH (*J.*, 1951, 920) reported a study of the absorption spectrum of keten $CH_2{:}C{:}O$, in the far ultra-violet. The present paper describes the spectrum of the *iso*electronic molecule allene, $CH_2{:}C{:}CH_2$.

Experimental.—Allene (b. p. −35°) was prepared by heating Eastman Kodak 2 : 3-dibromopropene with zinc dust and alcohol (Kistiakowsky, Ruhoff, Smith, and Vaughan, *J. Amer. Chem. Soc.*, 1936, **58**, 146). The crude allene was condensed in a liquid-nitrogen trap and was purified by re-distilling it three times in a high-vacuum system. Absorption bands of methylacetylene or propylene were absent from the spectrum.

The spectrum was photographed with a normal-incidence spectrograph, with the Lyman continuum as background. The grating, kindly lent by Dr. W. C. Price, was of glass and gave a dispersion of about 8 Å/mm.

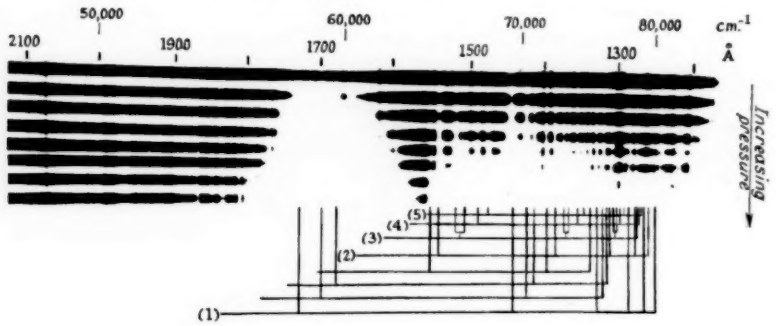
Description and Analysis of the Spectrum.—The spectrum is shown in the figure. To long wave-lengths of 1200 Å, the most intense absorption occurs between 1800 and 1600 Å ($\lambda_{max.}$ *ca.* 1710 Å). A number of bands is present in this region. Precise measurement is impossible, partly because of the diffuseness of the bands and partly because of the presence of emission lines in the Lyman continuum; but the order of magnitude of the positions and separations of some of the bands given in Table 1.

TABLE 1. *Separations of the bands in the* 1800—1600-Å *region* (*all as cm.*$^{-1}$).

57 800	58 310	58 500	58 820	59 560	60 240	60 700	61 300	61 960	62 500	63 100
	190									
510		510	740	680	460	600	660	540	600	

If it is assumed for the moment that the bands represent vibrational parts of a single electronic transition, a main frequency of 610 ± 100 cm.$^{-1}$ is involved. One or two bands representing a smaller frequency (~200 cm.$^{-1}$) also appear. Because of its intensity, the electronic transition in this region is certainly an allowed one and occurs from the vibrationless ground state. By the selection rules, therefore, the two frequencies must correspond

The absorption spectrum of allene in the vacuum ultra-violet.



to totally symmetrical (a_1) vibrations of the upper state. By analogy with ethylene and other derivatives of ethylene and because the excitation is probably that of an electron in the C–C–C bonds, the main frequency probably represents the a_1 C=C=C valency vibration reduced by the excitation from its value of 1071 cm.$^{-1}$ in the ground state (Herzberg, " Infra-red and Raman Spectra," van Nostrand, 1945). The proportionate reduction in ethylene (1623 to ~1370 cm^{-1}; ratio 0·8) and in keten (1120 to ~860 cm.$^{-1}$; ratio 0·8) is rather smaller than in allene (1071 to 610 ± 100 cm.$^{-1}$; ratio 0·5—0·7), but the only other ground state a_1 frequencies of allene are considerably higher (1432 and 2993 cm.$^{-1}$) and represent essentially C–H stretching and bending. It does not seem likely that the low subsidiary frequency can represent one of these a_1 vibrations. Possibly it represents two quanta of a non-totally symmetrical vibration; this would be equivalent, so far as symmetry is concerned, to an a_1 vibration. Suitable vibrations to choose would be either the twisting vibration (b_1, probably 820 cm.$^{-1}$ in the ground state) of the two CH_2 groups about the C=C=C axis or the degenerate bending vibration (*e*, perhaps 852 cm.$^{-1}$ in the ground state) of the chain H_2>C=C=C<H_2. It has been concluded (Price, Teegan, and Walsh, *loc. cit.*) that the corresponding excited-state frequency of keten probably represents a H_2>C=C=O bending vibration. In this connection it should be remembered that keten and allene are *iso*electronic with carbon dioxide. Now there is a strong theoretical expectation (see Mulliken, *Rev. Mod. Physics*, 1942, **14**, 204; Walsh, in the press) and some experimental evidence (Gaydon, " Spectroscopy and Combustion Theory," Chapman and Hall, 2nd Edn., 1948) that in certain low-lying excited states the carbon dioxide molecule, in its equilibrium form, is bent. It may well be therefore that, in the equilibrium form of

the excited state of allene (or keten) referred to above, the C·C·C (or C·C:O) chain is not linear; and therefore that the excitation tends to arouse bending vibrations of the chain. On the other hand, the short spacing in the corresponding absorption region of ethylene (*ca.* 400 cm.$^{-1}$) probably represents a twisting vibration of the two CH_2 groups about the C–C axis, since the excited state involved probably has a considerably reduced resistance to twisting (Mulliken, *Rev. Mod. Physics*, 1942, **14**, 265). The CH_2 planes in certain excited states of allene may tend to twist relative to each other; and excitation to these states may arouse the twisting vibration.

It is quite possible, however, that more than one electronic transition is involved in the 1800—1600 Å region, so that some of the separations recorded in Table 1 may be of electronic rather than of vibrational origin. This possibility is referred to again below.

To the long wave-length side of the 1800—1600 Å region, continuous absorption stretches from *ca.* 2030 to 1800 Å; it appears at a pressure several times greater than that required to bring out the 1710 Å absorption peak. At wave-lengths short of 1600 Å a pair of strong bands occurs at *ca.* 1540 Å with weaker bands to either side. Moderately strong bands lie at *ca.* 1520, *ca.* 1490, and *ca.* 1477 Å. A particularly strong band lies at 1446 Å and is followed by a considerable number of bands gradually decreasing in intensity until they disappear between 1250 and 1200 Å. At wave-lengths short of 1225 Å, except for a single stronger band at *ca.* 1204 Å and certain bands due to residual traces of oxygen in the spectrograph, only strong continuous absorption is observed.

All the bands in the spectrum are diffuse. Analysis is therefore difficult, but certainly the bands from 1446 to 1250 Å have the look of Rydberg bands, gradually getting weaker and closer together until they reach an ionization limit between 1250 and 1200 Å. By taking the 1446-Å band as one member of a Rydberg series proceeding to such a limit, it is possible to pick out four other bands which approximately conform to the expression,

$$\nu_0^n = 82\,210 - \boldsymbol{R}/(n - 1{\cdot}06)^2 \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad (1)$$

Table 2 shows the observed and calculated frequencies (cm.$^{-1}$). The agreement is about as good as could be expected in view of the diffuseness of the bands. Apart from this agreement, there is little doubt of the reality of series (1), partly because it yields an ionization limit (1216 Å) in the expected region and especially because the term values of its members agree closely with those of the members of the strongest Rydberg series found with many other molecules containing C=C groups. Thus the quantum defect of the best-developed series in the ethylene spectrum is 1·09 (see Price and Tutte, *Proc. Roy. Soc.*, *A*, 1940, **174**, 207) and that of the keten Rydberg series (known to be due to excitation of an electron largely, if not entirely, localized originally in the C=C group) is 1·07 (Price, Teegan, and Walsh, *loc. cit.*).

TABLE 2. *Observed and calculated frequencies (cm.$^{-1}$) of the bands of series* (1).

n	$\nu_{obs.}$	$\nu_{calc.}$	$\nu_{obs.} - \nu_{calc.}$	$\nu_{C_3H_4}$	$\nu_{C_3H_4} - \nu_{allene}$
3	*ca.* 57 800	53 053	*ca.* +4750	57 340	*ca.* −460
4	69 163	69 514	− 351	71 790	2627
5	75 153	75 141	+ 12	77 600	2547
6	77 702	77 713	− 11	80 215	2513
7	79 100	79 100	0	81 625	2525
8	79 856	79 932	− 76	—	—
∞	82 210	—	—	84 750	2540

Since series (1) represents excitation of an electron from an orbital compounded from *L*-shell atomic orbitals, one expects it to begin with a $n = 3$ member. The calculated position for this member lies between 1800 and 1900 Å, but one expects a considerable deviation of $\nu_{obs.}$ from $\nu_{calc.}$ because the comparatively low excitation implies that the size of the excited orbital cannot be vast compared to the nuclear framework of the molecule. On grounds of intensity, the 1800—1600-Å transition seems the only reasonable choice.

This leaves the 1540 Å doublet unassigned. It is very likely that it represents the first member of a second Rydberg series. Indeed it is possible to pick out bands lying between the successive members of series (1) which approximately fit the formula,

$$\nu_0^n = 82\,190 - \boldsymbol{R}/(n - 0{\cdot}70)^2 \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad (2)$$

The agreement between observed and calculated frequencies is given in Table 3. The 1540-Å doublet is a poor fit in this series but (*a*) this is not unreasonable for a first member

TABLE 3. *Observed and calculated frequencies (cm.$^{-1}$) of the bands of series (2).*

n	$\nu_{obs.}$	$\nu_{calc.}$	$\nu_{obs.} - \nu_{calc.}$	n	$\nu_{obs.}$	$\nu_{calc.}$	$\nu_{obs.} - \nu_{calc.}$
3	64 705	61 446	+ 3259	6	78 278	78 283	−5
4	72 081	72 113	− 32	7	79 426	79 425	+1
5	76 258	76 255	+ 3				

and (*b*) on grounds of intensity and position it seems the most reasonable choice as first member. The reality of series (2) is supported by the facts that it gives practically the same limit as series (1), that in the spectrum of ethylene a Rydberg series of nearly the same term values (quantum defect 0·6) occurs (see Price and Tutte, *loc. cit.*), and that it begins, as expected, with an $n = 3$ member.

The separations of the bands at *ca.* 1520, *ca.* 1490, and *ca.* 1477 Å from each other and from the 1540-Å electronic transition, considered in relation to the magnitude of the ground state C=C=C totally symmetrical frequency, make it unlikely that the bands are vibrational in nature. More probably, they each represent electronic transitions inaugurating other Rydberg series proceeding to the same limit as series (1) and (2). One can pick out a recurring pattern of at least three fairly strong bands between the successive n and $(n + 1)$ members of series (2) and (1), respectively. The recurring, but rapidly converging, pattern strengthens belief in the 1520-, 1490-, and 1477-Å bands' representing separate electronic transitions. The series beginning with the *ca.* 1520-Å band has the approximate formula,

$$\nu_0^n = 82\,190 - \boldsymbol{R}/(n - 0{\cdot}55)^2 \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad (3)$$

Its higher members, because of their diffuseness, become indistinguishable from the bands of what appears to be a second series of closely similar formula. The latter series begins with a very diffuse band which is partially obscured by emission lines and lies at *ca.* 1511 Å. Table 4 gives the observed and the calculated frequencies for the means of corresponding members of these two series.

TABLE 4. *Observed and calculated frequencies (cm.$^{-1}$) for the bands of series (3).*

n	ν_{obs}		$\nu_{calc.}$	$\nu_{obs.} - \nu_{calc.}$	n	$\nu_{obs.}$		$\nu_{calc.}$	$\nu_{obs.} - \nu_{calc.}$
3	65 808 66 188	mean = 65 998	63 918	+2080	5	76 460 76 772	mean = 76 616	76 648	−32
4	72 724 73 092	mean = 72 908	72 970	−62	6		78 529	78 495	+34
					7		79 566	79 552	+14

The series beginning with the *ca.* 1490-Å band has the approximate formula (4) and

$$\nu_0^n = 82\,200 - \boldsymbol{R}/(n - 0{\cdot}40)^2 \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad (4)$$

Table 5 shows the agreement between observed and calculated frequencies.

TABLE 5. *Observed and calculated frequencies (cm.$^{-1}$) for the bands of series (4).*

n	$\nu_{obs.}$	$\nu_{calc.}$	$\nu_{obs.} - \nu_{calc.}$	n	$\nu_{obs.}$	$\nu_{calc.}$	$\nu_{obs.} - \nu_{calc.}$
3	67 108	65 967	+1141	6	Obscured	78 701	—
4	73 721	73 733	− 12	7	79 635	79 681	−46
5	77 057	77 014	+ 43				

The series beginning with the *ca.* 1477-Å band has the approximate formula (5) and

$$\nu_0^n = 82\,210 - \boldsymbol{R}/(n - 0{\cdot}30)^2 \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad (5)$$

Table 6 shows the agreement between observed and calculated frequencies.

TABLE 6. *Observed and calculated frequencies (cm.$^{-1}$) for the bands of series (5).*

n	$\nu_{obs.}$	$\nu_{calc.}$	$\nu_{obs.} - \nu_{calc.}$	n	$\nu_{obs.}$	$\nu_{calc.}$	$\nu_{obs.} - \nu_{calc.}$
3	67 726	67 157	+569	5	77 280	77 242	+38
4	74 240	74 194	+ 46	6	78 828	78 832	− 4

The $n = 3$ member deviates considerably from the calculated position in each of these series, but it is satisfactory to note that the deviation decreases as the height of the excitation increases, *i.e.*, in the order series (1), (2), (3), (4), (5).

The existence of series (5) completes the parallel with ethylene; for in the ethylene spectrum a third and weak Rydberg series is observed, of quantum defect 0·3 (see Price and Tutte, *loc. cit.*).

At wave-lengths just longer than the 1540-Å doublet (at 64 362 cm.$^{-1}$), a weaker band occurs. The intensity is too high for it to be plausibly interpreted as a transition from a vibrational level of the ground state to the upper state of the 1540-Å transition. It appears to represent another electronic transition that inaugurates still another Rydberg series. Bands that appear to represent $n = 4$ and $n = 5$ members occur at 71 506 and 76 084 cm.$^{-1}$. Judged from the latter bands, the quantum defect lies between 0·75 and 0·80.

Two fairly strong bands (at *ca.* 1426 and *ca.* 1415 Å) lying between the $n = 4$ members of series (1) and (2) remain to be considered. They again probably represent separate electronic transitions. Their term values with respect to the ionization potential are too low for them to be interpreted as $n = 3$ members of further series. They must be $n = 4$ members of such series; and the only bands that can plausibly be interpreted as $n = 3$ members are two of those in the 1700-Å region. One or two higher members of each can be picked out, from which it appears that the quantum defect for both series is about 0·90.

The above classification covers practically all the bands in the spectrum.

Discussion.—The conclusion from the above analysis is that a large number of separate electronic transitions is present in the spectrum and that these can practically all be arranged into numerous Rydberg series all converging to the same limit. None of the series can be followed very far, but the cumulative evidence is very strong in favour of an ionization limit close to 82 200 cm.$^{-1}$. This corresponds to 10·19 v. An electron impact determination of the first ionization potential of allene has yielded the value 9·9 $\pm$ 0·2 v (Delfosse and Bleakney, *Phys. Review*, 1939, **56**, 256). A theoretical calculation of the ionization potential by Parr and Taylor (*J. Chem. Physics*, 1951, **19**, 497) gave the value 10·4 v. The ionization potential of 10·19 v for allene is to be compared with the values 10·50 and 9·60(5) v which are the corresponding limits for ethylene and keten, respectively.

Although the first ionization potential of allene is considerably less than that of ethylene, the first Rydberg bands are hardly shifted in passing from ethylene to allene. This is brought out in Table 2. The members of series (1) from $n = 4$ upwards suffer an almost constant shift relative to the corresponding bands in ethylene; but the $n = 3$ band is hardly shifted at all. A very similar phenomenon was observed in the spectrum of keten (Table 6 of Price, Teegan, and Walsh, *loc. cit.*). It implies that the lowering of the ionization potential in allene and keten is primarily due to a stabilization of the $C_3H_4^+$ or $C_2H_2O^+$ ions, respectively, relatively to the $C_2H_4^+$ ion. Only when the upper state is so highly excited that it resembles the ion does the stabilization show itself. The stabilization is presumably caused by the tendency of the electrons in the CH_2 "ϕ" group-orbital or in the O 2ϕ lone-pair orbital to occupy the place vacated in the C=C bond by the ionized electron. One can understand therefore why the lowering in allene should be less than that in keten, for one would expect the CH_2 electrons (if only because of their positions in space) to be less available than the O lone-pair electrons.

The following is a list of the Rydberg series which appear to be present in the spectrum :

(*a*)	one series of quantum defect	1·06
	two series " "	*ca.* 0·90
(*b*)	one series of quantum defect	0·75 to 0·80
	one series " "	0·70
	two series " "	*ca.* 0·55
(*c*)	one series of quantum defect	0·40
	one series " "	0·30

It is not unlikely that more series even than this are present, represented by weaker bands. Weak bands at wave-lengths just short of the *ca.* 1477 Å band seem particularly

likely to represent $n = 3$ members of other series with small quantum defects (~0·2). The types of Rydberg series likely to be found can be divided into series of allowed transitions to upper states built from *ns*, *np*, or *nd* orbitals on the carbon atoms. The magnitudes of the quantum defects make it probable that the series grouped as (*a*) are all to upper states built from *ns* orbitals; that those grouped as (*b*) are all (*np*) series; and that those grouped as (*c*) or which have even smaller quantum defects are (*nd*) series. A full discussion of the magnitudes of quantum defects in molecular Rydberg series will be given elsewhere. Suffice it to say for the moment that the defects of the allene (or ethylene) series are expected to be similar to those of Rydberg series observed or expected in the spectrum of free carbon atoms. It is for this reason that the series in (*a*), (*b*), and (*c*) have term values close to those of the three similar series found in the spectrum of ethylene.

The existence of so many different Rydberg series in the allene spectrum is in full accord with what one might expect. The most weakly bound electrons of the allene ground state lie in an (*e*) orbital which involves out-of-phase overlap of a "*p*" CH_2 group-orbital and a "π" C–C orbital. If V_d symmetry is assumed for the upper states of allene, there are several possible states to which transition from the ground state is allowed and which can be built from each of the types of orbital *ns*, *np*, and *nd*. For example, three non-degenerate orbitals can be built from *s* atomic orbitals on the carbon atoms, the resulting transitions being all $^1E \leftarrow\!\!- {}^1A_1$ (*i.e.*, two-fold degenerate) and all allowed. Similarly, numerous upper states to which transition from the ground state is allowed can be built from *p* atomic orbitals on the carbon atoms, especially since the *p* orbitals may be oriented in different ways with respect to the nuclear symmetry. These transitions include both $^1E \leftarrow\!\!- {}^1A_1$ and $^1B_2 \leftarrow\!\!- {}^1A_1$ symmetry types. If, further, one takes into account the possibility, referred to above, that in some of the upper states the C·C·C chain may not be linear or that the CH_2 planes may be twisted relatively to each other in the equilibrium form, the degeneracy of $^1E \leftarrow\!\!- {}^1A_1$ transitions may be split and still further series of transitions may occur. It becomes clear that the existence of so many Rydberg series is not surprising but to be expected.

The probability that several (*ns*) series exist, all having their $n = 3$ members in the 1800—1600-A region, makes it clear that, even apart from the diffuseness of the bands, a full analysis of the region is likely to be complicated.

All the bands from 1800 Å onwards seem best interpreted as Rydberg transitions. The weaker continuous absorption to wave-lengths longer than 1800 Å is best interpreted as due to intra-valency-shell transitions. In certain other molecules (*e.g.*, acetylene) where a clear distinction between Rydberg and non-Rydberg transitions is possible, the non-Rydberg transitions also require a considerably higher appearance pressure than the Rydberg ones. It is expected that the absorption regions observed in the spectrum of allene shall correspond to (though they lie at shorter wave-lengths than) those observed in the spectrum of ethylallene. An absorption curve for the long-wave-length end of the ethylallene spectrum has been published by Carr and Stücklen (Seventh Summer Conference on Spectroscopy, Wiley, New York, 1940, p. 128). Judged from this, the continuous absorption to wave-lengths longer than 1800 Å in allene represents at least three and perhaps five separate transitions. In ethylallene the first of these transitions is represented by a "step-out" at *ca.* 2560 Å with log $\varepsilon \sim 0$. The second is represented by a steep rise (between *ca.* 2500 and 2380 Å) to a maximum (of log $\varepsilon \sim 2{\cdot}8$) between *ca.* 2330 and 2270 Å. A rough absorption curve that we have plotted from data obtained by Lind and Livingston (*J. Amer. Chem. Soc.*, 1933, **55**, 1036) indicates that the corresponding steep rise in the allene spectrum occurs around 2330—2230 Å. Lind and Livingston write of appreciable absorption occurring some 40—80 Å to long wave-lengths of this steep rise: such absorption may be due to the allene analogue of the ethylallene 2560 Å "step out." The third region of the ethylallene spectrum is represented by a smaller rise in the absorption curve to a fairly flat absorption region between *ca.* 2050 and 1950 Å (log $\varepsilon \sim 3{\cdot}1$ or 3·2). (Further, rather stronger, absorption stretching to 1600 Å may belong to the same transition or, more probably, to further transitions.) Judged from our photographs, the corresponding transition in allene appears to cause a rise in the absorption curve around 2030 Å. The allene maximum at *ca.* 1710 Å appears to correspond to a maximum (log $\varepsilon \sim$

3·8) at *ca.* 1800 Å for ethylallene. These values are very approximate, but are of some interest since Parr and Taylor (*loc. cit.*) have recently attempted to calculate the position of certain intra-valency-shell transitions of allene; they give 5·1 v (2430 Å) for the mean height of the first singlet and triplet excited states.

We are indebted to the Royal Society and the Chemical Society for grants in aid of equipment, to Dr. W. C. Price for the generous loan of a diffraction grating, and to the Department of Scientific and Industrial Research and to the Anglo-Iranian Oil Company for financial support to one of us (L. H. S.).

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163. *Favoured Ring Forms in Acetals of the Polyhydric Alcohols.*

By S. A. BARKER and E. J. BOURNE.

Published data concerning the condensations of polyhydric alcohols with acetaldehyde, benzaldehyde, and formaldehyde are reviewed, and rules are presented which enable the products resulting from such condensations to be predicted. The graded hydrolysis and acetolysis of acetals are discussed in the light of these rules. A comment is made on the epimerisation of dimethylene acetals of saccharic acids.

WE have recently reviewed published data on the synthesis and structural analysis of cyclic acetals and ketals derived from the polyhydric alcohols, and, on the basis of the information thus collected, we now present certain "rules," which enable the pattern of condensation between a given carbonyl compound and a given polyhydric alcohol to be predicted. It has long been known that the course of such a reaction is determined both by the relative configurations of the hydroxyl groups in the polyhydric alcohol (cf. the methylene derivatives of sorbitol, dulcitol, and mannitol) and by the structure of the carbonyl component (cf. the methylene and *iso*propylidene derivatives of mannitol).

In order to simplify the presentation and discussion of these rules, a code system will be introduced, whereby the position and size of an acetal ring can be indicated precisely. The Greek letters, α, β, and γ, will signify the relative positions, along the carbon chain of the polyhydric alcohol, of the two hydroxyl groups engaged in the cyclisation, and C and T will indicate whether these two groups are disposed *cis* or *trans* in the usual Fischer projection formula; C and T will be required only when *both* alcohol groups are secondary. Thus, a system in which an alkylidene residue spans two secondary hydroxyl groups, located on adjacent carbon atoms and having a *trans*-orientation, contains an αT-ring, whereas a β-ring is present when one of the alcohol groups concerned is primary and the other is situated on the β-carbon atom.

A study of the methylene acetals of proven structure derived from dulcitol, mannitol, sorbitol, and ribitol enabled Hann and Hudson (*J. Amer. Chem. Soc.*, 1944, **66**, 1909) to reach certain conclusions, which, when expressed in terms of our code, were as follows: (*a*) a βC-ring is favoured, but a βT-ring is not; (*b*) a β-ring is favoured; (*c*) a βC-ring is preferred to a β-ring; (*d*) a γT-ring is favoured, but a γC-ring is not; (*e*) an α-ring may be formed when a β-ring is not permissible. Later, Ness, Hann, and Hudson (*J. Amer. Chem. Soc.*, 1948, **70**, 765) added a rider to the effect that a γT-ring (previously believed, from considerations of the behaviour of methylene acetals during acetolysis, to be highly favoured) may not be formed when β- and βC-rings also are permissible. The American workers observed, too, that these rules were compatible with the data then available for benzylidene acetals of the polyhydric alcohols. The Hann–Hudson rules have long been recognised as being an outstanding contribution in this field, and have been of great value in the interpretation of the problems of acetal formation and in the prediction of the structures of acetals of the polyhydric alcohols; their applications are far too well known to require enumeration here.

In the light of all the relevant information concerning the acetals of the tetritols and their higher homologues which has been garnered since the introduction of the above rules, it is now possible to extend them to cover virtually all known cases of the formation of benzylidene, ethylidene, and methylene derivatives of the polyhydric alcohols. The extended rules are: (1) the first preference is for a βC-ring; (2) the second for a β-ring; (3) the third for an α-, αT-, βT-, or γT-ring; (4) in methylenation, a βT-ring takes precedence over an αT- or a γT-ring; (5) in benzylidenation and ethylidenation, an αT-ring takes precedence over a βT- or a γT-ring; (6) rules (4) and (5) may not apply when one (or both) of the carbon atoms carrying the hydroxyl groups concerned is already part of a ring system.

Rule (5) is to be regarded as tentative because of the small number of examples upon which it can be based. We know of no case in which the condensation of an aldehyde with a polyhydric alcohol affords a γ-, αC-, or γC-ring. It should be noted that the participation of two alcohol groups, possessing a *trans*-orientation, in acetal formation is made possible by free rotation within the carbon skeleton of the polyhydric alcohol, a situation which is not encountered when the carbon atoms carrying these hydroxyl groups are already part of a ring system; it is for this reason that it is necessary to include rule (6).

In Table 1 are listed, with four exceptions, all the benzylidene, ethylidene, and methylene acetals of known structure, derived from the tetritols and their higher homologues, of which we have a record; every one of these 50 compounds complies with the above modified rules. A decision whether rule (6) should, or should not, be applied is not necessary in any of the cases cited, but the question does arise in the four exceptions, namely, in the syntheses of 1 : 3-2 : 5-dimethylene rhamnitol (Haskins, Hann, and Hudson, *J. Amer. Chem. Soc.*, 1945, **67**, 1800), 3 : 5-benzylidene-1 : 4-anhydrosorbitol (Bashford and Wiggins, *J.*, 1948, 299), 3 : 5-benzylidene 6-chloro-1 : 4-anhydro-6-deoxysorbitol (Montgomery and Wiggins, *J.*, 1948, 237), and 3 : 5-benzylidene 6-bromo-1 : 4-anhydro-6-deoxysorbitol (Overend, Montgomery, and Wiggins, *J.*, 1948, 2201).

The rules predict that allitol, dulcitol, and iditol should form diacetals, but not triacetals, with the three aldehydes under consideration, and in fact no triacetals have yet been prepared from the first two of these hexitols. However, there were reports in the early literature that iditol affords a tribenzylidene (last reference, *Ann. Chim. Phys.*, 1907, **10**, 450) and a trimethylene derivative (last reference, *Compt. rend.*, 1906, **143**, 352). In view of the failure of Hann and Hudson (*J. Amer. Chem. Soc.*, 1945, **67**, 602) to repeat the preparation of the latter compound, these reports should be discounted until further evidence in support of them is forthcoming.

A second point arising out of Table 1 concerns the methylene derivatives of talitol. Our rules indicate that talitol should furnish 2 : 4-methylene, 1 : 3-2 : 4-dimethylene, and 1 : 3-2 : 4-5 : 6-trimethylene derivatives, and indeed Hann, Haskins, and Hudson (*ibid.*, 1947, **69**, 624) have prepared the mono- and tri-acetals, but, in place of the predicted diacetal, they obtained two isomers, which they thought to be 2 : 3 : 4 : 5- * and 1 : 3-4 : 6-dimethylene talitol. We believe that the former compound (yield, 2%) was really 2 : 4-3 : 5-dimethylene allitol and that it arose from a trace of allitol impurity in the syrupy sample of talitol employed in the synthesis. Our reasons are as follows: (1) the direct methylenation of allitol is known to yield the 2 : 4-3 : 5-dimethylene derivative (Wolfrom, Lew, and Goepp, *ibid.*, 1946, **68**, 1443); (2) the D-talitol sample used had been prepared from α-D-altropyranose penta-acetate by treatment with sodium methoxide in methanol and subsequent hydrogenation, so epimerisation may well have occurred to a small extent; and (3) the melting point and specific rotation of the "dimethylene talitol," of its diacetate, and of its ditoluene-*p*-sulphonate, agree well with those recorded for the corresponding members of the allitol series (cf. Hann, Haskins, and Hudson, *loc. cit.*; Wolfrom, Lew, and Goepp, *loc. cit.*). Hudson and his colleagues noted that the data upon which they assigned the 1 : 3-4 : 6-structure to the second dimethylene hexitol did not exclude the 1 : 2 : 4 : 6- and 1 : 3 : 5 : 6-structures, but all of these possibilities are at variance with the modified rules. Since this compound is, as far as we are aware, the only one which definitely infringes the rules, a more detailed study of its structure would be desirable.

* In this paper the form "2 : 3 : 4 : 5-structure" has been used whenever the evidence available did not serve to distinguish between the 2 : 3-4 : 5-, 2 : 4-3 : 5-, and 2 : 5-3 : 4-structures.

TABLE 1. *Syntheses of benzylidene, ethylidene, and methylene acetals which conform with the modified rules.*

Parent hydroxy-compound	Types of rings formed	Acetal derivative	Reference
Arabitol	β	1 : 3-Benzylidene	*J. Amer. Chem. Soc.*, 1943, **65**, 1663
,, , 1 : 5-dibenzoyl	αT	2 : 3-Benzylidene	,, ,, ,,
Ribitol	βC	2 : 4-Methylene	*Ibid.*, 1944, **66**, 1906
,,	βC, β	1 : 3-2 : 4-Dimethylene	,, ,, ,,
Xylitol	—	1 : 2 : 3 : 4-Dibenzylidene	,, 1947, **69**, 1667
,,	βC, β	1 : 3-2 : 4-Dimethylene	,, 1944, **66**, 670
,, , 2 : 4-methylene	β	1 : 3-Benzylidene	,, 1950, **72**, 561
,, , 1-deoxy-2 : 4-methylene	β	3 : 5-Methylene	,, ,, ,,
Allitol	βC, βC	2 : 4-3 : 5-Dimethylene	,, 1946, **68**, 1443
Dulcitol	β, β	1 : 3-4 : 6-Dibenzylidene	,, 1942, **64**, 132
,, ...	β, β	1 : 3-4 : 6-Dimethylene	,, 1942, **64**, 986
,, , 1 : 6-dibenzoyl	—	2 : 3 : 4 : 5-Dibenzylidene	,, 1942, **64**, 136, 137
,, , 1 : 6-ditrityl	—	2 : 3 : 4 : 5-Dibenzylidene	,, 1939, **61**, 1827
,, , 2 : 5-dibenzyl	β, β	1 : 3-4 : 6-Dimethylene	,, 1942, **64**, 986
Iditol	βC, βC	2 : 4-3 : 5-Dimethylene	,, 1945, **67**, 602
Mannitol ...	β, β, γT	1 : 3-2 : 5-4 : 6-Triethylidene	*J.*, 1951, 2708
,,	β, β	1 : 3-4 : 6-Dimethylene	*J. Amer. Chem. Soc.*, 1943, **65**, 2215
,,	β, β, γT	1 : 3-2 : 5-4 : 6-Trimethylene	,, ,, ,,
,, , 1 : 6-dibenzoyl	αT	3 : 4-Benzylidene	*Ber.*, 1933, **66**, 931
,, ,,	—	2 : 3 : 4 : 5-Dibenzylidene	*J. Amer. Chem. Soc.*, 1943, **65**, 1419
,, ,,	βT, βT	2 : 4-3 : 5-Dimethylene	*J.*, 1944, 58, 364
,, , 1 : 2 : 5 : 6-tetrabenzoyl	αT	3 : 4-Benzylidene	*Ber.*, 1933, **66**, 931
,, ,, ,,	αT	3 : 4-Ethylidene	*J.*, 1951, 2708
,, , 1 : 6-dibenzoyl 3 : 4-benzylidene	γT	2 : 5-Methylene	*J. Amer. Chem. Soc.*, 1943, **65**, 2215
,, , 1 : 6-dibenzoyl 2 : 5-methylene	αT	3 : 4-Benzylidene	,, ,, ,,
,, , 1 : 6-dibromo-1 : 6-dideoxy	βT, βT	2 : 4-3 : 5-Dimethylene	*J.*, 1948, 2201
,, , 1 : 6-dichloro-1 : 6-dideoxy	αT	3 : 4-Ethylidene	*J.*, 1946, 384
,, ,, ,,	—	2 : 3 : 4 : 5-Diethylidene	,, ,,
,, ,, ,,	βT, βT	2 : 4-3 : 5-Dimethylene	*J. Amer. Chem. Soc.*, 1943, **65**, 67
,, , 1 : 6-dideoxy-1 : 6-di-iodo	βT, βT	2 : 4-3 : 5-Dimethylene	*J.*, 1946, 384
,, , 1 : 6-dimethyl	βT, βT	2 : 4-3 : 5-Dimethylene	,, ,,
Sorbitol	βC	2 : 4-Benzylidene	*Ber.*, 1935, **68**, 1582
,,	βC, β	1 : 3-2 : 4-Dibenzylidene	*J. Amer. Chem. Soc.*, 1944, **66**, 837
,,	βC, β, α	1 : 3-2 : 4-5 : 6-Tribenzylidene	,, ,, ,,
,,	βC, β	1 : 3-2 : 4-Diethylidene	*Ibid.*, 1947, **69**, 849
,,	βC, β, α	1 : 3-2 : 4-5 : 6-Triethylidene	*J.*, 1948, 1933
,,	βC, β	1 : 3-2 : 4-Dimethylene	*J. Amer. Chem. Soc.*, 1944, **66**, 665
,,	βC, β, α	1 : 3-2 : 4-5 : 6-Trimethylene	*J.*, 1944, 517
,, , 1 : 6-dibenzoyl	βC, βT	2 : 4-3 : 5-Dibenzylidene	*J.*, 1946, 488
,, ,,	βC, βT	2 : 4-3 : 5-Dimethylene	*J. Amer. Chem. Soc.*, 1944, **66**, 1898
,, , 1 : 6-dichloro-1 : 6-dideoxy	—	2 : 3 : 4 : 5-Dibenzylidene	*J.*, 1948, 237
,, , 5 : 6-dimethyl	βC, β	1 : 3-2 : 4-Dimethylene	*J.*, 1944, 517
6-Deoxysorbitol	βC, β	1 : 3-2 : 4-Dimethylene	*J. Amer. Chem. Soc.*, 1944, **66**, 1235
,, , 2 : 4-methylene 1-tosyl	βT	3 : 5-Methylene	*Ibid.*, p. 1901
Talitol	βC	2 : 4-Methylene	*Ibid.*, 1947, **69**, 624
,,	βC, β, α	1 : 3-2 : 4-5 : 6-Trimethylene	,, ,, ,,
Gluco-*gulo*-heptitol	βC	3 : 5-Benzylidene	*Ibid.*, 1946, **68**, 1769
,, ,,	βC	3 : 5-Methylene	,, ,, ,,
Perseitol	β, β	1 : 3-5 : 7-Dibenzylidene	*Ibid.*, 1948, **70**, 765
,,	β, β	1 : 3-5 : 7-Dimethylene	,, ,, ,,

It should be mentioned that the benzylidenation of 1 : 6-dibenzoyl dulcitol (Haskins, Hann, and Hudson, *J. Amer. Chem. Soc.*, 1942, **64**, 136, 137) and the ethylidenation of 1 : 6-dichloro-1 : 6-dideoxymannitol (Wiggins, *J.*, 1946, 384) both afford two isomeric

diacetals, but in neither case is it yet known whether they differ in the position or in the stereoisomerism of the acetal groups.

An alternative way of assessing the relative stabilities of acetal groups of different types is to consider the products resulting when di- and tri-acetals are submitted to partial hydrolysis with aqueous acid. From the list of such cases given in Table 2, it can be seen that the order of stability is: $\beta C > \beta > \alpha$ and γT, which is precisely the order already deduced. (N.B. α- and γT-Rings cannot occur together in any acetal derived from a polyhydric alcohol containing fewer than seven carbon atoms.)

TABLE 2. *Graded acidic hydrolysis of benzylidene, ethylidene, and methylene acetals.*

Parent compound	Order of ring scission: 1st	2nd	3rd	Reference
1 : 3-2 : 4-5 : 6-Tribenzylidene sorbitol	α	β	βC	*J. Amer. Chem. Soc.*, 1944, **66**, 837
1 : 3-2 : 5-4 : 6-Triethylidene mannitol	γT	β	β	*J.*, 1951, 2708
1 : 3-2 : 4-Diethylidene sorbitol	β	βC	—	*J.*, 1948, 1933
2 : 4-3 : 5-Dimethylene allitol	βC	βC	—	*J. Amer. Chem. Soc.*, 1946, **68**, 1443
1 : 3-2 : 4-5 : 6-Trimethylene sorbitol	α	β	βC	*J.*, 1944, 517

TABLE 3. *Graded acetolysis of methylene acetals.*

Parent compound: Alcohol component	Positions of acetal groups	Rings broken	Rings retained	References (all in *J. Amer. Chem. Soc.*)
Ribitol	1 : 3-2 : 4	β	βC	1944, **66**, 1906
Xylitol	2 : 4-3 : 5	β	βC	1944, **66**, 670
,, , 1-mesyl	2 : 4-3 : 5	β	βC	1950, **72**, 561
,, , 1-tosyl	2 : 4-3 : 5	β	βC	,, ,,
2 : 5-Dibenzoyl dulcitol	1 : 3-4 : 6	β, β	None	1943, **65**, 2215
Iditol	2 : 4-3 : 5	None	βC, βC	1945, **67**, 602
Mannitol	1 : 3-2 : 5-4 : 6	β, β	γT	1943, **65**, 2215
,, , 6-deoxy	1 : 3-2 : 5	β	γT	1945, **67**, 1800
Sorbitol	1 : 3-2 : 4	β	βC	1944, **66**, 665
,,	2 : 4-3 : 5	βT	βC	1944, **66**, 1898
,,	1 : 3-2 : 4-5 : 6	α, β	βC	1944, **66**, 665
,, , 6-deoxy	1 : 3-2 : 4	β	βC	1944, **66**, 1235
Talitol	1 : 3-2 : 4-5 : 6	α, β	βC	1947, **69**, 624
,, , 2 : 5-diacetyl	1 : 3-4 : 6(?)	β, β	None	,, ,,

TABLE 4. *Syntheses of* iso*propylidene derivatives of the polyhydric alcohols.*

Parent hydroxy-compound	*iso*Propylidene deriv.	Reference
Xylitol	3 : 5(?)	*Chem. Zvesti*, 1949, **3**, 146
,,	1 : 2-3 : 5(?)	,, ,,
,,	2 : 3 : 4 : 5(?)	*J. Amer. Chem. Soc.*, 1944, **66**, 73
Dulcitol	2 : 3 : 4 : 5*	*Ibid.*, 1939, **61**, 611, 2432
,,	2 : 3 : 5 : 6*	,, ,,
Mannitol	1 : 2	*Ber.*, 1933, **66**, 1394
,,	1 : 2-5 : 6	*J. Amer. Chem. Soc.*, 1939, **61**, 2607
,,	1 : 2-3 : 4-5 : 6	*J.*, 1946, 13
,, , 1 : 6-dibenzoyl	3 : 4	*Ber.*, 1932, **65**, 1055
,, , 1 : 6-dichloro-1 : 6-dideoxy	3 : 4	*J.*, 1946, 384
,, ,, ,, ,,	2 : 3 : 4 : 5	,, ,,
,, , 1 : 2 : 5 : 6-tetrabenzoyl	3 : 4	*Ber.*, 1933, **66**, 931
Sorbitol	1 : 2	*J. Amer. Chem. Soc.*, 1950, **72**, 2404
,,	1 : 2-5 : 6	,, ,, ,,
,,	1 : 2-3 : 4-5 : 6	,, ,, ,,

* Certain experiments reported by Pizzarello and Freudenberg (*J. Amer. Chem. Soc.*, 1939, **61**, 611) still require to be interpreted in the light of these structures.

One might suppose that the limited acetolysis of methylene acetals with an ice-cold mixture of acetic anhydride, acetic acid, and 1—2% sulphuric acid, a reaction which has been used so effectively by Hudson and his colleagues in their studies of the structures of these acetals, might also confirm this order of stability, and, up to a point, this is so, for examples are given in Table 3 of cases in which α-, β-, and βT-rings are broken before

βC-rings; however, the expected scission of a γT-ring in preference to a β-ring does not occur. As was pointed out by Hudson and his co-workers (references in Table 3), it seems that the major factor governing the rate of acetolysis of a methylene compound is whether or not the methylene group is engaged at a primary position. Two compounds in which this over-riding factor is eliminated provide an interesting contrast, when subjected to acetolysis under identical conditions. Thus, 2 : 4-3 : 5-dimethylene iditol is not attacked (both βC-rings stable), whereas 2 : 4-3 : 5-dimethylene sorbitol suffers scission of the βT-ring, but not of the βC-ring.

The foregoing observations would seem to have a direct bearing on the demonstration by Haworth, Jones, Stacey, and Wiggins (*J.*, 1944, 61, 364) that the 2 : 4-3 : 5-dimethylene derivatives of D-glucosaccharic and D-mannosaccharic acids can both be epimerised to 2 : 4-3 : 5-dimethylene L-idosaccharic acid. In the former case, inversion occurs at $C_{(5)}$ (in the βT-ring), but not at $C_{(2)}$ (in the βC-ring); in the latter case, there is inversion at both $C_{(2)}$ and $C_{(5)}$ (both in βT-rings). The product, which presumably is stable under these conditions, possesses two βC-rings.

Current knowledge regarding favoured ring structures in *iso*propylidene derivatives of the polyhydric alcohols leaves much to be desired, for the information available is meagre (see Table 4), and, moreover, is contradictory as far as the condensations of xylitol and dulcitol with acetone are concerned. Nevertheless, it is clear that the above rules do not apply, and that there is a marked preference for the formation of five-membered rings. We have no record of a condensation between acetone and a derivative of a polyhydric alcohol yielding a seven-membered ring; six-membered rings are rare but they probably exist in 2 : 3 : 4 : 6-di*iso*propylidene 1 : 5-anhydro-D-mannitol (*Adv. Carbohydrate Chem.*, 1950, **5**, 191) and in the di*iso*propylidene derivative of 2 : 4-benzylidene D-sorbitol (*Ber.*, 1935, **68**, 18, 1377). All that can be said with assurance at present is that α- and αT-rings are permissible, and that, in synthesis, the former takes precedence over the latter. If the graded acidic hydrolysis of 1 : 2-3 : 4-5 : 6-tri*iso*propylidene mannitol (*Ber.*, 1934, **67**, 1969; *Helv. Chim. Acta*, 1934, **17**, 1574; *J.*, 1946, 13) be any guide, an α-ring is hydrolysed more readily than an αT-ring. The hydrolysis of 1 : 2-3 : 4-5 : 6-tri*cyclo*hexylidene D-mannitol follows the same course as that of the *iso*propylidene analogue (*J.*, 1950, 786).

In conclusion, it may be noted that the carbonyl compounds can be divided, on the basis of the ring types favoured in their condensations with the polyhydric alcohols, into two groups, one including benzaldehyde, acetaldehyde, and formaldehyde, and the other, acetone and *cyclo*hexanone. It is too early to say whether this present sharp division between aldehydes and ketones is purely fortuitous or whether it is likely to be maintained when the condensation products derived from other carbonyl compounds are subjected to structural analysis.

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164. *Tetrahydropyran-3 : 4-diol and Tetrahydro-2 : 2 : 5 : 5-tetramethylfuran-3 : 4-diol.*

By Oscar Heuberger and L. N. Owen.

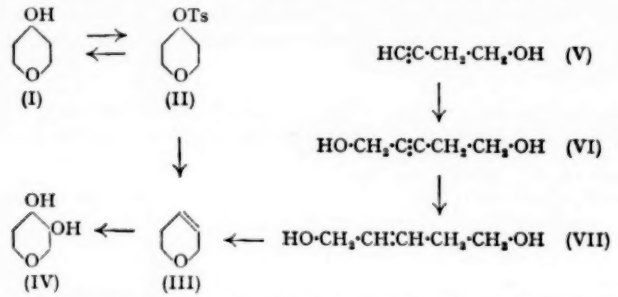
The sulphonyloxy-group in the toluene-*p*-sulphonate of tetrahydropyran-4-ol undergoes replacement by iodine, acetoxy-, etc., much more readily than in the alicyclic series.

A convenient synthesis of 2 : 3-dihydro-6-pyran, from acetylenic precursors, is described.

The *cis*- and the *trans*-form of each of the diols mentioned in the title has been prepared by hydroxylation of the corresponding unsaturated compound with neutral potassium permanganate or performic acid. The isolation and properties of 3 : 4-epoxytetrahydro-2 : 2 : 5 : 5-tetramethylfuran (IX) are recorded.

In connection with studies on alicyclic glycols (Clarke and Owen, *J.*, 1950, 2108, and earlier papers), an extension into the field of heterocyclic glycols is envisaged, and, as a simple analogue of *cyclo*hexane-1 : 2-diol, the preparation of tetrahydropyran-3 : 4-diol (IV) has been investigated. The *trans*-form was briefly described by Paul and Tchelitcheff (*Compt. rend.*, 1947, **224**, 1722, where it is incorrectly named 2 : 3-dihydroxytetrahydropyran) as obtained by hydrolysis of the 3 : 4-epoxide derived by oxidation of 5 : 6-dihydro-2-pyran (III) with perbenzoic acid, but it is evident that by the use of the appropriate hydroxylation methods it should be possible to prepare both the *cis*- and the *trans*-diol directly from the unsaturated compound (III). The latter was obtained by Paul and Tchelitcheff (*loc. cit.*) by dehydrobromination of 4-bromotetrahydropyran, but an alternative method appeared to be the elimination of toluene-*p*-sulphonic acid from the ester (II), particularly since *cyclo*hexyl toluene-*p*-sulphonate gives *cyclo*hexene, and no *cyclo*hexanol, when treated with alkali (Hückel and Frank, *Annalen*, 1930, **477**, 143).

Tetrahydropyran-4-ol (I) readily formed a crystalline toluene-*p*-sulphonate (II), but when this was heated with aqueous potassium hydroxide it not only gave the dihydropyran (III) but also underwent simple hydrolysis and regenerated a considerable proportion of (I); replacement, at the expense of elimination, therefore occurs more readily than with the alicyclic analogue. This was also shown in the reactions of (II) with alcoholic potassium



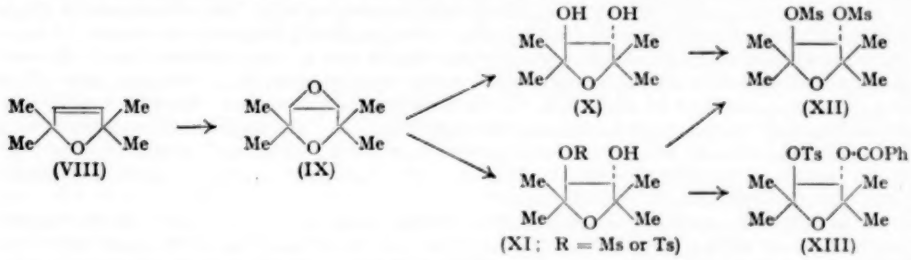
acetate, alcoholic lithium chloride, and sodium iodide in acetone (cf. Clarke and Owen, *loc. cit.*), the corresponding acetate, chloride (together with some ethyl ether), and iodide being formed as well as the unsaturated product. The replacement with iodine occurred particularly readily, and gave a 67% yield of distilled tetrahydro-4-iodopyran, in marked contrast to the similar reaction with *cyclo*hexyl toluene-*p*-sulphonate (cf. Tipson, Clapp, and Cretcher, *J. Org. Chem.*, 1947, **12**, 133).

These results, coupled with the inaccessibility of tetrahydro-4-hydroxypyran itself, made it necessary to devise a new synthesis of the dihydropyran, and the following method was found to be suitable. But-3-yn-1-ol (V), prepared by condensation of acetylene and ethylene oxide in liquid ammonia (cf. Macallum, U.S.P. 2 125 384), was converted into

pent-2-yne-1 : 5-diol (VI) by reaction with formaldehyde in the presence of the cuprous hydroxide catalyst described by Heilbron, Jones, and Sondheimer (*J.*, 1947, 1586); an alternative procedure, involving the interaction of gaseous formaldehyde with the Grignard compound of but-3-yn-1-ol gave a smaller yield of the desired product. Quantitative hydrogenation of the pentynediol over a palladium catalyst deposited on charcoal, calcium carbonate, or barium sulphate, gave no indication of a change of rate after the absorption of 1 mol. of hydrogen, but by interruption of the hydrogenation at that point a product was obtained which contained the required pent-2-ene-1 : 5-diol (VII) since when heated under reduced pressure with sulphuric acid it gave 5 : 6-dihydro-2-pyran (III) in 34% yield; this could probably be improved by further study of the semihydrogenation conditions.

The *cis*- and the *trans*-tetrahydropyran-3 : 4-diol were readily prepared by hydroxylation of the dihydropyran with neutral permanganate and performic acid, respectively. Both were oils, but they were characterised as the crystalline ditoluene-*p*-sulphonates.

An unusual result was obtained in the hydroxylation of 2 : 5-dihydro-2 : 2 : 5 : 5-tetramethylfuran (VIII). With neutral permanganate it gave the expected *cis*-tetrahydro-2 : 2 : 5 : 5-tetramethylfuran-3 : 4-diol, but with performic acid not only the *trans*-diol (X) but also the epoxide (IX) was obtained. Both stereoisomers of the diol were solid, and they were further characterised by conversion into crystalline disulphonates. Epoxides



are considered to be intermediates in the hydroxylation of olefins with performic acid (cf. Swern, Billen, Findley, and Scanlan, *J. Amer. Chem. Soc.*, 1945, **67**, 1786), but normally do not survive the strongly acidic conditions; the present instance appears to be the first case of the isolation of the epoxide, which suggests that the ethylene oxide ring in (IX) is more stable than usual. Nevertheless, the oxide was hydrolysed to the *trans*-diol (X) when heated with sulphuric acid in aqueous dioxan, and reacted readily with methanesulphonic acid and with toluene-*p*-sulphonic acid to give the monosulphonates (XI) of the *trans*-diol; these were liquids, but they were characterised by conversion into the crystalline *trans*-dimethanesulphonate (XII) and *trans*-benzoate toluene-*p*-sulphonate (XIII).

Experimental

γ-Pyrone was prepared by decarboxylation of chelidonic acid (*Org. Synth.*, Coll. Vol. II, p. 126) by heating it at 250—260°, in batches of 10 g., with copper powder (20 g.) and 20-mesh pumice (10 g.). The organic layer from the distillate was taken up in ether, dried, evaporated, and distilled to give *γ*-pyrone, b. p. 97°/12 mm. The average yield was 64% (cf. Willstätter and Pummerer, *Ber.*, 1904, **37**, 3745).

Tetrahydropyran-4-ol.—*γ*-Pyrone (22 g.) in ethanol (250 c.c.) was hydrogenated at 100° and 60 atm. during 8 hours by use of Raney nickel catalyst (5 g.). The product, isolated by evaporation of the filtered solution, was dissolved in ether and dried (Na_2SO_4). Distillation gave tetrahydropyran-4-ol (17·5 g., 79%), b. p. 84—85°/12 mm., n_D^{20} 1·4580.

Toluene-p-*sulphonate.* A solution of toluene-*p*-sulphonyl chloride (32 g.) in dry pyridine (50 c.c.) was added during 1 hour to a stirred solution of tetrahydropyran-4-ol (17·2 g.) in dry pyridine (50 c.c.) at 0°; the mixture was set aside at 0° overnight. The *toluene*-p-*sulphonate* (27 g., 63%) was precipitated by addition of ice, and crystallised from aqueous ethanol in colourless needles, m. p. 56° (Found: S, 12·3. $C_{12}H_{16}O_4S$ requires S, 12·5%).

Methanesulphonate. Tetrahydropyran-4-ol (2·86 g.) was treated with methanesulphonyl

chloride (3·2 g.) in pyridine (10 c.c.). After 12 hours at 0°, the reaction mixture was diluted with chloroform (50 c.c.), washed with dilute hydrochloric acid and water, dried (Na_2SO_4), and evaporated. The *methanesulphonate* (1·75 g., 35%) crystallised from ethanol in needles, m. p. 49—50° (Found : C, 40·3; H, 6·7; S, 17·5. $C_6H_{12}O_4S$ requires C, 40·0; H, 6·7; S, 17·8%).

Reactions of the Toluene-p-*sulphonate.*—(a) *With aqueous alkali.* The toluene-*p*-sulphonate (12·4 g.) was heated under reflux with 5% aqueous potassium hydroxide (100 c.c.) for 2 hours. After being cooled and saturated with salt, the reaction mixture was continuously extracted with ether for 2 days. Fractionation of the dried ethereal solution gave two main fractions : 5 : 6-dihydro-2-pyran (1·16 g., 28·6%), b. p. 92—100°, n_D^{24} 1·4438, and tetrahydropyran-4-ol (1·37 g., 27·8%), b. p. 88—90°/14 mm., n_D^{24} 1·4553. The latter was further identified as its toluene-*p*-sulphonate, m. p. and mixed m. p. 56°.

(b) *With sodium iodide.* The toluene-*p*-sulphonate (2 g.) and sodium iodide (3 g., 2·5 equiv.) in acetone (30 c.c.) were refluxed for 24 hours. The dark brown solution was filtered from sodium toluene-*p*-sulphonate (1·4 g., 92·5%) and was concentrated through a Fenske column to small bulk, the distillate being unsaturated. The semi-solid residue was diluted with water (10 c.c.) and extracted with ether (200 c.c.). The extracts were washed with aqueous sodium thiosulphate and water to remove free iodine, dried (Na_2SO_4), and evaporated under reduced pressure to a pale yellow oil, which on distillation gave *tetrahydro*-4-*iodopyran* (1·1 g., 67%), b. p. 79—80°/12 mm., n_D^{21} 1·5471 (Found : I, 59·85. C_5H_9OI requires I, 59·9%). The same product was also obtained (yield, 36%) by similar treatment of the methanesulphonate.

(c) *With potassium acetate.* The toluene-*p*-sulphonate (5 g.) and potassium acetate (5 g.) in ethanol (60 c.c.) were refluxed for 20 hours. The potassium toluene-*p*-sulphonate (3·5 g., 85%) was filtered off and an aliquot part of the filtrate was titrated with sodium hydroxide (phenolphthalein); the acidity corresponded to the formation of 42% of acetic acid. The mixture was concentrated to small bulk, the distillate being unsaturated. The solid residue was dissolved in water (10 c.c.) and extracted with ether (200 c.c.). The dried extracts, on fractional distillation, gave the acetate of tetrahydropyran-4-ol (0·8 g., 29%) as a colourless oil, b. p. 75—76°/12 mm., n_D^{22} 1·4368 (Found : C, 58·5; H, 8·7. Calc. for $C_7H_{12}O_3$: C, 58·3; H, 8·4%). Baker (*J.*, 1944, 296) gives b. p. 47·5°/1 mm.

(d) *With lithium chloride.* A solution of the toluene-*p*-sulphonate (4 g.) and lithium chloride (2 g.) in ethanol (70 c.c.) was refluxed for 16 hours and then concentrated to small bulk, the distillate being unsaturated. The residue was diluted with water (20 c.c.) and extracted with ether (250 c.c.). The dried (Na_2SO_4) extracts were evaporated to an oil (0·37 g.), b. p. 44—45°/12 mm., n_D^{25} 1·4492, which was a mixture of 4-chloro- and 4-ethoxy-tetrahydropyran (Found : C, 54·7; H, 8·7; Cl, 19·6. Calc. for a mixture of 67% C_5H_9OCl and 33% $C_7H_{14}O_2$: C, 54·7; H, 8·6; Cl, 19·7%).

Pent-2-*yne*-1 : 5-*diol.*—(i) A cuprous hydroxide catalyst (Heilbron, Jones, and Sondheimer, *loc. cit.*) was prepared by treatment of cuprous chloride (12 g.) in 12% hydrochloric acid (180 c.c.) with 40% aqueous potassium hydroxide (180 c.c.). The precipitate was collected and washed with water; it was then transferred, while still moist, to a mixture of but-3-yn-1-ol (52 g.), 40% formaldehyde (80 g.), water (24 c.c.), and calcium carbonate (0·8 g.), which was stirred on a steam-bath for 4 days under nitrogen. The semi-solid product was collected on a filter and washed with aqueous ethanol (1 : 1) (500 c.c.). The filtrate and washings were concentrated and distilled, to give *pent*-2-*yne*-1 : 5-*diol* (48·8 g., 66%) as a colourless oil, b. p. 120°/0·5 mm., n_D^{24} 1·4890 (Found : C, 60·1; H, 7·9. $C_5H_8O_2$ requires C, 60·0; H, 8·05%).

(ii) A solution of methylmagnesium bromide was prepared from methyl bromide (172 g.) and magnesium (32·4 g.) in dry ether (800 c.c.). The ether was removed by distillation, dry benzene (1000 c.c.) being simultaneously added, and to the resulting solution but-3-yn-1-ol (40 g.) dissolved in dry benzene (50 c.c.) was slowly added, with stirring, during 2½ hours. Formaldehyde gas, generated by heating paraformaldehyde (60 g.), was introduced during a further 2 hours, stirring being maintained for several hours afterwards (cf. Raphael and Sondheimer, *J.*, 1950, 2100). The resulting complex was decomposed in the usual way with ammonium chloride solution, and the product on distillation afforded pent-2-yne-1 : 5-diol (8·75 g., 18%), b. p. 90—95°/0·03 mm., n_D^{21} 1·4895.

5 : 6-*Dihydro*-2-*pyran.*—A solution of pent-2-yne-1 : 5-diol (47·4 g.) in ethanol (250 c.c.) was hydrogenated at room temperature and pressure with a 5% palladium–charcoal catalyst (5 g.). When 1 mol. of hydrogen had been absorbed (4 hours) the reaction was stopped. Evaporation of the filtered solution then gave pent-2-ene-1 : 5-diol (39·3 g), b. p. 91—92°/0·5 mm., n_D^{21} 1·4759. This material (18 g.), with 20% sulphuric acid (1 c.c.), was heated in nitrogen at

120°/12 mm., the distillate being collected in a receiver cooled in liquid air. After 4 hours the end of the reaction was indicated by a sudden frothing of the dark viscous residue. The distillate was allowed to melt, and the organic layer was removed, dried (Na_2SO_4), and distilled to give **5 : 6-dihydro-2-pyran** (5·1 g., 34%), b. p. 94—95°, n_D^{15} 1·4480. Paul and Tchelitcheff (*loc. cit.*) give b. p. 93—94°, n_D^{19} 1·4477.

cis-*Tetrahydropyran*-3 : 4-*diol*.—A solution of potassium permanganate (10 g.) and magnesium sulphate (7·5 g.) in water (200 c.c.) was added dropwise with vigorous stirring to a solution of 5 : 6-dihydro-2-pyran (6·6 g.) in ethanol (150 c.c.) during 2½ hours, the temperature being kept between −15° and −20°. The manganese dioxide was filtered off and thoroughly washed with boiling water (400 c.c.) and the combined filtrates were filtered again through kieselguhr and concentrated under reduced pressure to small bulk. The residue was saturated with salt and continuously extracted with ether, to yield *cis*-tetrahydropyran-3 : 4-diol as a colourless viscous oil (1·6 g.), b. p. 84—87°/0·3 mm., n_D^{21} 1·4875. On treatment with toluene-*p*-sulphonyl chloride in pyridine it gave the cis-*ditoluene*-p-*sulphonate*, which crystallised from ethanol in needles, m. p. 131—132° (Found : C, 53·3; H, 5·2; S, 15·0. $C_{19}H_{22}O_7S_2$ requires C, 53·5; H, 5·2; S, 15·0%).

trans-*Tetrahydropyran*-3 : 4-*diol*.—5 : 6-Dihydro-2-pyran (6·9 g.) was added to pure formic acid (90 g.) and 30% hydrogen peroxide (11 g.) with vigorous stirring. The temperature rose to 45° and was so maintained by external cooling and later by heating in a water-bath during 4 hours. The reaction mixture was concentrated under reduced pressure, and the residue heated on the steam-bath with 10% sodium hydroxide (100 c.c.) for an hour and again concentrated to small bulk. The residue was continuously extracted with ether and furnished *trans*-tetrahydropyran-3 : 4-diol (5·95 g.) as a colourless oil, b. p. 100—102°/0·5 mm., n_D^{23} 1·4861. Paul and Tchelitcheff (*loc. cit.*) give b. p. 158—159°/9 mm., n_D^{18} 1·4873. Reaction with toluene-*p*-sulphonyl chloride in pyridine gave the trans-*ditoluene*-p-*sulphonate*, which crystallised from ethanol in needles, m. p. 161—162° (Found : C, 53·8; H, 5·5; S, 14·8%).

Reaction of 2 : 5-*Dihydro*-2 : 2 : 5 : 5-*tetramethylfuran with Performic Acid*.—The dihydrotetramethylfuran (Johnson and Johnson, *J. Amer. Chem. Soc.*, 1940, **62**, 2615) (7·9 g.), pure formic acid (68 g.), and 30% hydrogen peroxide (8·4 g.) were stirred at 40° for 3½ hours. Formic acid was then distilled off, and the dark brown residue was basified with sodium hydroxide, heated under reflux for an hour, and distilled under reduced pressure. The distillate was saturated with salt and extracted with ether; the extracts were dried (Na_2SO_4) and concentrated to give 3 : 4-*epoxytetrahydro*-2 : 2 : 5 : 5-*tetramethylfuran* (2·3 g., 25%) as a colourless, camphoraceous oil, b. p. 90—91°/100 mm., n_D^{22} 1·4190, which solidified below 20° (Found : C, 67·3; H, 10·2. $C_8H_{14}O_2$ requires C, 67·6; H, 9·9%). The alkaline residue from the distillation was dissolved in water and extracted with ether (400 c.c.); evaporation of the dried (Na_2SO_4) extracts gave trans-*tetrahydro*-2 : 2 : 5 : 5-*tetramethylfuran*-3 : 4-*diol* (0·6 g.) which crystallised from light petroleum (b. p. 80—100°) in needles, m. p. 158—159° (Found : C, 60·2; H, 10·15. $C_8H_{16}O_3$ requires C, 60·0; H, 10·1%). The *dimethanesulphonate*, prepared by treatment of the diol with excess of methanesulphonyl chloride in pyridine, crystallised from methanol in plates, m. p. 104° (Found : C, 37·95; H, 6·3; S, 19·9. $C_{10}H_{20}O_7S_2$ requires C, 37·95; H, 6·4; S, 20·3%).

Ring-fission of 3 : 4-*Epoxytetrahydro*-2 : 2 : 5 : 5-*tetramethylfuran*.—(i) The epoxide (0·15 g.) was heated for 1½ hours at 100° with dioxan (1·5 c.c.) and N-sulphuric acid (3 c.c.). The solution was then neutralised with barium carbonate, filtered, and evaporated to a solid residue of *trans*-tetrahydro-2 : 2 : 5 : 5-tetramethylfuran-3 : 4-diol (0·1 g.), m. p. and mixed m. p. 158—159° after recrystallisation from light petroleum (b. p. 80—100°).

(ii) A solution of the epoxide (1 g.) and toluene-*p*-sulphonic acid (1·2 g.) in dry ether (80 c.c.) was set aside at 0° for 24 hours, then washed with sodium hydrogen carbonate solution, dried (Na_2SO_4), and evaporated to an oil. A portion of this crude monotoluene-*p*-sulphonate was treated with benzoyl chloride in pyridine at 0° overnight, and gave the *benzoate toluene*-p-*sulphonate* of the *trans*-diol, which crystallised from ethanol in needles, m. p. 141—142° (Found : C, 62·8; H, 6·3. $C_{22}H_{26}O_6S$ requires C, 63·1; H, 6·3%).

(iii) Freshly distilled methanesulphonic acid (0·45 g.) was added to the epoxide (0·6 g.). The mixture became hot and viscous. The crude monomethanesulphonate thus obtained failed to crystallise; on treatment in pyridine solution with methanesulphonyl chloride it gave, in good yield, the *trans*-dimethanesulphonate, m. p. and mixed m. p. 104°.

cis-*Tetrahydro*-2 : 2 : 5 : 5-*tetramethylfuran*-3 : 4-*diol*.—A solution of potassium permanganate (6·25 g.) and anydrous magnesium sulphate (4·7 g.) in water (125 c.c.) was added dropwise with vigorous stirring to a solution of crude dihydrotetramethylfuran (6·3 g., b. p. 84—100°) in ethanol (150 c.c.) during 2 hours, the temperature being kept at 0°; manganese dioxide was then filtered

off and washed with ethanol. The filtrates were evaporated under reduced pressure to a solid residue, which was extracted with ether, dried (Na_2SO_4), concentrated, and distilled to yield cis-*tetrahydro*-2 : 2 : 5 : 5-*tetramethylfuran*-3 : 4-*diol*, which crystallised from light petroleum (b. p. 40—60°) in needles (0·6 g.), m. p. 93—94° (Found: C, 60·2; H, 10·3. $C_8H_{16}O_3$ requires C, 60·0; H, 10·1%). Treatment of the diol with toluene-*p*-sulphonyl chloride in pyridine gave the *ditoluene*-p-*sulphonate*, which crystallised from methanol in flattened needles, m. p. 131—132° (Found: C, 56·5; H, 6·0; S, 13·6. $C_{22}H_{28}O_7S_2$ requires C, 56·4; H, 6·0; S, 13·7%).

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165. *Interaction of Hydrogen Halides and* n-*Butyl Phosphites.*

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Rates of dealkylation of three *n*-butyl esters of phosphorous acid by means of hydrogen halides have been determined in ethereal solution and in absence of ether. It is shown that the rates for a given ester are with respect to the hydrogen halides in the order HI > HBr ≫ HCl, and for a given halide are with respect to the three esters in the order $P(OR)_3 \gg PHO(OR)_2 >$ $PHO(OH)(OR)$. The possibility of studying such systems by kinetic methods was also investigated. The results have an important bearing on the understanding of the course of interaction of inorganic non-metallic halides and alcohols.

RATES of stepwise dehalogenation of non-metallic inorganic halides and rates of stepwise dealkylation of the corresponding esters by hydrogen halides must be known in order to give detailed descriptions of reaction sequences in alcohol–inorganic non-metallic halide systems. A superimposed factor is the degree of reactivity of the alcoholic carbon atom, and useful progress cannot be made without recognising at least a rough classification into alcohols such as butan-1-ol and octan-2-ol of " ordinary " reactivity and those such as 1-phenylethanol and *tert.*-butyl alcohol which have a very much more reactive alcoholic carbon atom. Successive replacement of chlorine in phosphorus trichloride by alkoxyl, $PCl_2 \cdot OR$, $PCl(OR)_2$, $P(OR)_3$, followed by dealkylation, $P(OR)_3 + HCl \longrightarrow PHO(OR)_2 +$ RCl, appears to constitute the reaction sequence mainly, if not entirely, responsible for the formation of such alkyl chlorides as 1-chlorobutane and 2-chloro-octane (Gerrard, *J.*, 1940, 218, 1464; 1944, 85) under what may be termed ordinary experimental conditions. That the hydrogen atom in the so-called dialkyl hydrogen phosphites is attached to the phosphorus atom is supported by observations on vibrational spectra (Meyrick and Thompson, *J.*, 1950, 225), and the esters are therefore dialkyl phosphonates. The ready removal of one alkyl group from the trialkyl phosphite may therefore be correlated with the basic function of the lone pair of electrons on the phosphorus atom, a structural detail missing in four-covalent phosphorus systems and in boron and silicon systems (Gerrard and Lappert, *J.*, 1951, 1020, 2545; Gerrard and Woodhead, *J.*, 1951, 519).

Phosphorus tribromide–alcohol and phosphorus tri-iodide–alcohol systems tend to follow the same reaction sequences; but dealkylation of the dialkyl hydrogen phosphite is rapid enough to be effective in ordinary reaction times, and furthermore, there are signs that alkyl halide is also formed by other reactions involving the hydrogen halide (Gerrard, *J.*, 1945, 848; Berlak and Gerrard, *J.*, 1949, 2309). It must be emphasised that for more reactive alcohols (*e.g.*, *tert.*-butyl alcohol and 1-phenylethanol) the aforementioned sequences have not yet been clearly discerned; *e.g.*, *tert.*-butyl alcohol rapidly gives the alkyl chloride and phosphorous acid in practically 100% yield.

We have now examined the interaction of hydrogen halides with *n*-butyl phosphites for two reasons—to obtain more precise information about relative rates of reaction, and to

explore possibilities of applying the kinetic method to the further study of alcohol–phosphorus trihalide systems. Data for ethereal solutions at 25° are summarised in the table, the initial esters being tributyl phosphite and dibutyl hydrogen phosphite (phosphonate). Hydrogen chloride removed one butyl group from the tri-ester in a time during which removal of alkyl group from the product (di-ester) was not perceptible. Dealkylation of the di-ester proceeded very slowly, and this explains why the preparation of the hydrogen phosphite in accordance with the equation $3BuOH + PCl_3 = RCl + PHO(OBu)_2$ is practicable. Although the removal of one alkyl group from the tri-ester was rapidly effected by hydrogen bromide at −10° without observed incursion of further dealkylation, a plot of the data for the much slower dealkylation of the di-ester at 25° clearly shows that the removal of a second alkyl group (dealkylation of the product, mono-ester) proceeded to an observable extent soon after the beginning of the experiment. We estimate that dealkylation of the di-ester by hydrogen bromide proceeds 9 times as fast as that of the mono-ester under equivalent conditions.

Comparison of dealkylation rates expressed as the number of alkyl groups per mol. of n-*butyl phosphites removed in the stated time.*

Ester	Molality	HX	Molality	Time	No. of alkyl groups removed
Tri-	0·10	HCl	0·10	5 hours	0·5
Di-	0·50	HCl	1·00	1290 ,,	1·0
,,	0·65	,,	1·3	1260 ,,	1·0
Tri-	0·20	HBr	0·20	3 min.	1·0 (at −11°)
,,	0·075	,,	0·10	2 ,,	1·0 (at −10°)
Di-	0·25	,,	0·50	3 hours	1·0
				126 ,,	1·9
,,	0·10	,,	0·20	6 ,,	1·0
				224 ,,	1·96
,,	1·02	,,	0·39	1·3 ,,	0·38
Di-	0·025	HI	0·05	2 ,,	1·0
,,	0·04	,,	0·08	1 hour	0·9
				2 hours	1·2

We examined our data with a view to calculating specific rates, but concluded that study over a much more extensive field of conditions is necessary before precise statements can be made about the details of mechanism. This study is being continued.

Experiments performed with the reagents in absence of ether support the observations already described. The di-ester exothermally absorbed 1 mol. of hydrogen chloride, evolving approximately 4260 cal./mole; but dealkylation proceeded slowly, 0·5 mol. of alkyl group being removed during 4 days, and 0·75 mol. during 30 days. Furthermore, as dealkylation progressed, so the mixture was able to absorb more hydrogen chloride. This seems to show a ready initial interaction between the di-ester and halide not involving the final attachment of chlorine to the alkyl group. The mono-ester, on formation by dealkylation of the di-ester, can form a similar association with hydrogen chloride. Now, the tri-ester rapidly absorbed 2 mols. of hydrogen chloride exothermally, and after 10 days 1-chlorobutane was isolated in 39·6% yield. Similarly, the tri-ester and hydrogen bromide afforded 1-bromobutane in 72% yield after 2 days, whereas after 24 hours the corresponding reagents gave 1-iodobutane in 82·1% yield.

We conclude that the rates for a given ester are with respect to hydrogen halides in the order HI > HBr ⩾ HCl, and for a given halide are with respect to the three esters in the order $P(OR)_3 \geqslant PHO(OR)_2 > PHO(OH)(OR)$, and that the data now submitted contribute to the correlation of experimental conditions, relative proportions of reagents, and nature and amounts of products in the alcohol–phosphorus trihalide system.

Experimental

Rate of Interaction of Hydrogen Halides and n-*Butyl Phosphites in Ethereal Solution.*—Tri-*n*-butyl phosphite, d_4^{20} 0·9200 (Found: P, 12·8. Calc. for $C_{12}H_{27}O_3P$: P, 12·4%), and di-*n*-butyl hydrogen phosphite, b. p. 124—126°/20 mm. (Found: P, 15·8. Calc. for $C_8H_{19}O_3P$: P, 16·0%), were prepared as described by Gerrard (*loc. cit.*). An ethereal solution of the hydrogen halide

and the ester was kept in a thermostat, and samples were removed after the specified intervals of time. This was done by the slight application of pressure through a calcium chloride guard tube to the surface of the solution in the reaction flask. The sample was received in a tube (11·46 ml.) fitted with two taps. Halide ion was determined in the aqueous extract of each sample by Volhard's method. To prepare the solution, dry hydrogen halide was passed into anhydrous ether, the approximate concentration of the solution determined, and ether added to give approximately the concentration required; the actual concentration was then determined, the initial concentration, for the purpose of the experiment, being calculated by allowing for the volume change when the ester was added. The results are given in the following tables.

0·100 Molal tri-ester, 0·102 molal HCl at 25°.

Time, hours	0·25	0·5	0·75	1	1·5	2·5	3	4	5
HCl reacted, mole/l. $\times 10^4$	56	96	132	173	244	340	386	457	518

0·50 Molal di-ester, 1·00 molal HCl at 25°.

Time, hours	48	234	523	691	859	1070	1290	1644
HCl reacted, mole/l. $\times 10^3$	4	16	30	37	40	46	50	54

(When initial molality of HCl was 1·297, and that of the ester was 0·65, 0·64 mol./l. of HCl reacted in 1260 hours.)

0·200 Molal tri-ester, 0·204 molal HBr at −11°.

Time, min.	1	2	3	7	10	20
HBr reacted, mole/l. $\times 10^3$	170	187	193	200	202	204

0·075 Molal tri-ester, 0·10 molal HBr at −10°.

Time, min.	0·5	1	2	3	5	10	60
HBr reacted, mole/l. $\times 10^3$	44	65	72	74	74	75	75

[In 2 min. over 97% of the HBr corresponding to the reaction $HBr + P(OR)_3 \longrightarrow RBr + PHO(OR)_2$ had disappeared, but even after 60 min., the loss of HBr did not perceptibly exceed the amount required for that reaction, even though HBr was available for further attack on the hydrogen phosphite.]

0·25 Molal di-ester, 0·502 molal HBr at 25°.

Time, hours	0·5	1	1·5	2	2·5	3·5	4·5	6	8	30	54	78	126
HBr reacted, mole/l. $\times 10^3$	98	155	190	211	237	266	282	298	333	409	442	455	475

0·10 Molar di-ester, 0·208 molal HBr at 25°.

Time, hours	0·5	1	1·5	2	2·5	3	3·5	5
HBr reacted, mole/l. $\times 10^3$	18	36	46	52	59	70	74	88
Time, hours	6	55	80	106	152	224	272	320
HBr reacted, mole/l. $\times 10^3$	95	166	176	179	189	196	198	199

1·02 Molal di-ester, 0·386 molal HBr at 25°.

Time, min.	15	35	50	65	80
HBr reacted, mole/l. $\times 10^3$	193	290	335	375	380

0·025 Molal di-ester, 0·05 molal HI at 25°.

Time, min.	20	40	60	80	100	120	140	160	180	200	220
HI reacted, mole/l. $\times 10^4$	74	125	162	167	222	250	255	259	287	269	287

(By the time the equivalent of one alkyl group had been removed there was a serious liberation of free iodine.)

0·04 Molal di-ester, 0·08 molal HI at 25°.

Time, min.	20	40	60	80	100	120	140	160
HI reacted, mole/l. $\times 10^4$	168	270	354	387	410	480	499	504

[When the initial molality of di-ester was 0·015, and that of HI 0·03, the molality of the latter fell to 0·015 (corresponding to one alkyl group) in 4 hours.]

*Interaction of Di-*n*-butyl Hydrogen Phosphite and Hydrogen Halides in the Absence of Ether.*— The ester was weighed in a vessel fitted with a tube through which the hydrogen halide could be passed. The vessel was put into a thermostat (25°) and fitted with a trap kept at −10°. The gas was passed for the time stated, and the vessel and the trap were re-weighed. The contents were mixed with water, and the halide ion was estimated by Volhard's method.

Dry hydrogen chloride was passed into 2·2545 g. of ester for 15 minutes; the gain in weight of the reaction vessel was 0·4155 g., and that of the trap, 0·0160 g. Determination of chloride ion showed the presence of 0·4225 g. of hydrogen chloride. The amount of gas absorbed, but not permanently lost, is very nearly that required by the equimolar ratio (Calc.: 0·4242 g.). The

total increase in weight of 1·862 g. of ester after the gas had been passed for 6 hours was 0·3490 g., and the weight of hydrogen chloride present was, by titration, 0·3480 g. Again these weights correspond to an equimolar ratio.

It was noticed that when the gas was passed into the uncooled ester, there was a sudden rise in temperature, and the amount of heat evolved was estimated by adding a copper cylinder (5·62 g.) (at 100°) to 5·242 g. of ester in a specially constructed apparatus, the original temperature of which was 17·6°. The rise in temperature of the vessel and contents was 11·1°. Therefore the heat capacity of the vessel and ester was 3·43 cal./degree. The rise in temperature when hydrogen chloride was passed into 5·25 g. of ester was 33·6°, and this corresponds to 4260 cal./g.-mol. of ester.

Observations on the passage of dry hydrogen bromide into the ester are recorded below :

Time, min.	Wt. of ester, g.	Increase in wt. of trap, g.	Increase in wt. of vessel, g.	Wt. of HBr (by titrn.), g.	Wt. of HBr reacted, g.	Removal of one R group, %
20	0·8425	0·1205	0·4770	0·4664	0·1311	37
50	1·1610	0·0820	0·6550	0·4573	0·2797	58
85	0·7885	0·0910	0·5265	0·4083	0·2092	64

The absorption of hydrogen iodide was so quick that the rate could not be followed. The amount absorbed appeared to correspond with the removal of both butyl groups.

In order to study the interaction with hydrogen chloride over a longer period, a different technique was devised. The stated weight of the ester in a tube was saturated with hydrogen chloride, the tube was sealed, and the weight of gas absorbed determined. A number of such tubes were placed in a thermostat at 25°, and each tube was opened under a solution of silver nitrate after the stated interval of time. Chloride ion was determined by Volhard's method, and the results are recorded in the following table.

Time, days	Wt. of ester, g.	Wt. of HCl, g.	Wt. of HCl left, g.	Fraction of HCl reacted	Time, days	Wt. of ester, g.	Wt. of HCl, g.	Wt. of HCl left, g.	Fraction of HCl reacted
1	0·4965	0·0870	0·0781	0·10	11	0·5245	0·0910	0·0257	0·72
2	0·4290	0·0770	0·0610	0·21	14	0·5815	0·1020	0·0367	0·64
4	0·6605	0·1185	0·0582	0·51	21	0·6555	0·1185	0·0343	0·71
7	0·5470	0·0950	0·0354	0·63	30	0·5760	0·1010	0·0254	0·75

Isolation of the Alkyl Halides.—Hydrogen chloride (1·3555 g.) was rapidly absorbed by 4·6160 g. of the tri-ester, and this weight corresponds with almost 2 g.-mol. of the gas to 1 g.-mol. of the ester (Calc. : 1·43 g. HCl). The temperature rose rapidly to 35° despite attempts at cooling. It appears therefore that dealkylation of the first group was proceeding, and we were left with the molecular proportion of hydrogen chloride merely absorbed. After the capped absorption vessel had been at 25° for 24 hours, hydrogen chloride was again passed, but there was no further increase in weight. After a further 4 days at 25°, there was an increase in weight of 0·3280 g. when hydrogen chloride was again passed. 1-Chlorobutane (2·035 g., 39·8% yield, considering the three butyl groups), b.p. 76—78° (Found : Cl, 38·0. Calc. : Cl, 38·4%), was obtained from the reaction mixture after it had stood at 25° for a further 5 days.

In a similar way 4·609 g. of the tri-ester absorbed 4·3815 g. of hydrogen bromide during two days, and the reaction mixture separated into two layers. The top layer was soluble in water, and from the bottom layer, 1-bromobutane (5·49 g., 72%), b. p. 100—101° (Found : Br, 58·0. Calc. : Br, 58·4%), was isolated.

The amount of hydrogen iodide absorbed rapidly rose to 3 mols. for one mol. of the tri-ester. After 24 hours at 25°, the mixture had separated into two layers. From the bottom one, 1-iodobutane (4·88 g., 82·1%) (Found : I, 68·2. Calc. : I, 69·0%) was obtained.

NORTHERN POLYTECHNIC, LONDON, N.7. [*Received, November 13th*, 1951.]

166. *Researches on Monolayers. Part I. Molecular Areas and Orientation at Water Surfaces of Aromatic Azo-compounds containing Long Alkyl Chains.*

By C. H. Giles and E. L. Neustadter.

A series of twenty-two aromatic azo-compounds containing straight alkyl chains (C_{12}—C_{18}) and, in most cases, one hydroxy-group either *o*- or *p*- to the azo-group, has been examined for unimolecular film-forming properties on water. Condensed films are formed in all cases where a hydroxy-group is present and the alkyl chain has at least 16 carbon atoms, and in many cases where it has 12 carbon atoms. In absence of a hydroxy-group at least two azo-groups appear to be required to give the necessary water attraction for stable films to be formed. The molecules appear to be oriented in the films with the plane of the aromatic nuclei vertical, but the longer axis of this plane is in many cases tilted from the perpendicular at an angle depending on the nature and relative position of the various substituent groups.

A series of long-chain alkyl aromatic azo-compounds has been prepared, and their spreading properties on water have been examined. It is hoped to use these and similar compounds in monolayer reactions to study dye photolysis and the adsorption of dyes by fibres.

A large number of anthraquinone and azo-dyes containing long alkyl chains have been described (see Knight, *J. Soc. Dyers Col.*, 1950, **66**, 34) and several are in commercial use. These, however, are all water-solubilised by sulphonic acid groups. The dyes formed in the " Agfacolour " photographic film during development are also formed from intermediates containing long alkyl chains, incorporated in the emulsion during manufacture. These also contain a water-solubilising group, in some cases a sulphonic group (see, *e.g.*, Adams, " I.G. Farbenindustrie. The Manufacture of Intermediates and ' Colour Formers ' for Agfa Farbenfilm," B.I.O.S. Final Report No. 1605). Water-insoluble long-chain azo-compounds of the type used in the present work do not appear to have been studied previously.

It was expected that alkyl arylazo-compounds, with at least C_{12} chains and containing hydroxy-groups, would be film-forming. The presence of a phenolic group aids film formation; *e.g.*, *p*-alkylphenols, with straight chains of at least 12 carbon atoms, form condensed films (Adam, *Proc. Roy. Soc.*, 1923, *A*, **103**, 676; Adam, Berry, and Turner, *ibid.*, 1928, **117**, 532). The effect of an azo-group on monolayer formation has not been reported. At the outset of the present work three compounds (I, II, III) were prepared to determine whether this group has sufficient water-attraction to assist film formation. It was found that (III) readily forms condensed films, but neither (I) nor (II) does so; thus, a single azo-group has water-attracting properties, but they are less than those of, *e.g.*, the hydroxy-group. It was next found that condensed films are readily formed if the long-chain azo-compound has also a hydroxy-group in the molecule.

The compounds used in the present investigation (I—XXII) have been chosen partly for the availability of the intermediate products and partly for their suitability in showing the effect upon orientation of (*a*) the length of the alkyl chain attached to one of the aromatic nuclei, (*b*) the presence of hydroxy-groups *o*- or *p*- to the azo-group, (*c*) the presence of condensed ring systems in the molecule, and (*d*) the presence of water-attracting groups in the alkyl chain.

The results are shown in the table and Figs. 1—3.

Adam and his co-workers (*loc. cit.*) found that long-chain *p*-alkylphenols in monolayers have a molecular area of about 24 Å^2, consistent with close vertical packing of the benzene rings. The areas of the present compounds lie in the range 30—55 Å^2, and it is evident from a study of scale models that in these monolayers also the molecule is so oriented that the plane of the aromatic nuclei is vertical. The molecules are thus stacked

side by side like slices of toast in a rack. Whatever substituent groups may be present, the plane of the rings remains vertical, but the whole molecule may be tilted in this plane at an angle depending on the nature and relative position of the substituent groups.

In illustration, the probable orientations of pairs of molecules of three typical

FIG. 1. *o-Hydroxyazo-compounds.*

FIG. 2. *Bisazo- and o-hydroxyazo-compounds.*

FIG. 3. *p-Hydroxyazo-compounds.*

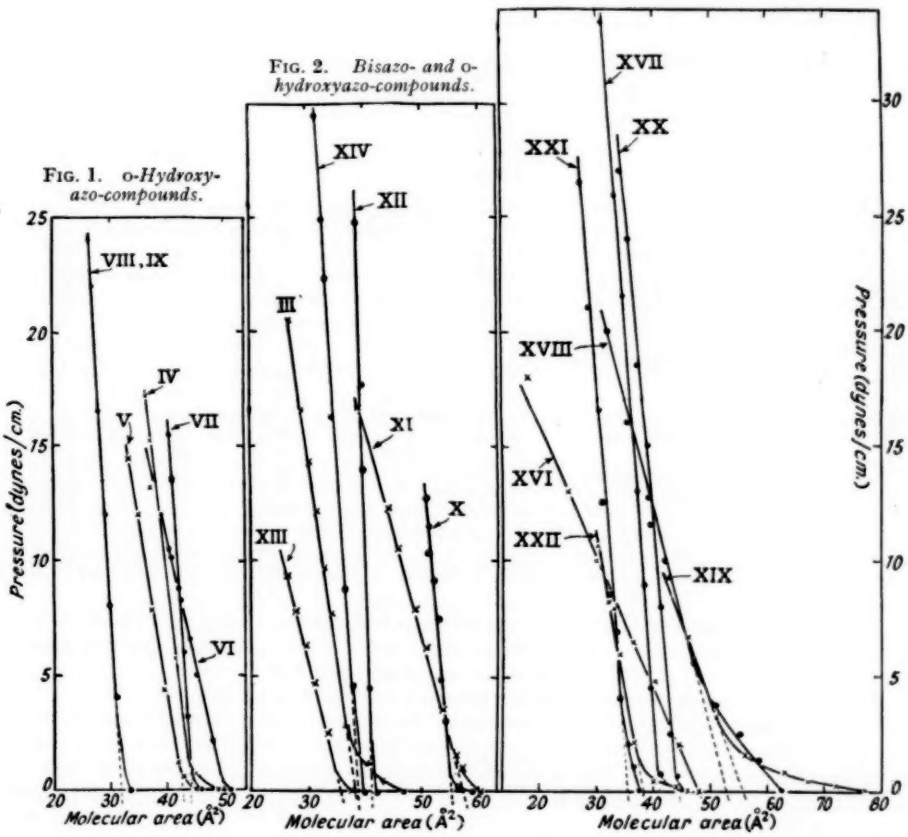
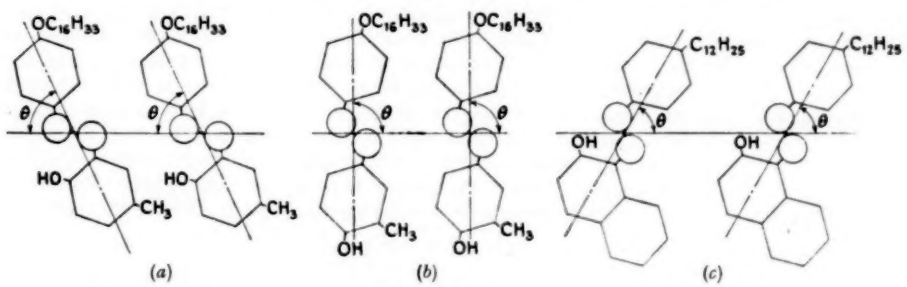


FIG. 4. *Orientation of typical* o- *and* p-*hydroxyazo-compounds at the water surface.*



(*a*) (XIII, $\theta = 65°$) (*b*) (XXI, $\theta = 90°$) (*c*) (V, $\theta = 65°$)

Molecular areas and orientation angles.

No.	Compound	Coupling component	Limiting area (Å²)	Area at zero compression (Å²) *	Probable angle of orientation to water surface
	Azo-compounds without hydroxy-groups.				
I	*p*-Dodecylazobenzene		No film formed		
II	4-Hexadecyloxyazobenzene		No film formed		
III	4′-Hexadecyloxybis(phenylazo)benzene		48	38	90°
	Hydroxyazo-compounds.				
	Diazo-component				
	o-Hydroxyazo-compounds.				
IV	*p*-Dodecylaniline	*p*-Cresol	49	44·5	45°
V	do.	β-Naphthol	45	42·5	60°
VI	do.	3-Phenanthrol	51	50	65°
VII	*p*-Hexadecylaniline	β-Naphthol	46	44·5	60°
VIII	Aniline	*p*-Hexadecylphenol	33	32	90°
IX	do.	*p*-Octadecylphenol	33	32	90°
X	Hexadecyl *m*-aminobenzoate	*p*-Cresol	59	55	80°
XI	do.	β-Naphthol	60	57	55°
XII	Hexadecyl *p*-aminobenzoate	do.	41·5	41	45°
XIII	*p*-Hexadecyloxyaniline	*p*-Cresol	37	35·5	65°
XIV	do.	β-Naphthol	39	38	55°
	p-Hydroxyazo-compounds.				
XV	*p*-Dodecylaniline	*o*-Cresol	No film formed		—
XVI	do.	α-Naphthol	48	48	70°
XVII	do.	α-Anthranol	*ca.* 46	41	90°
XVIII	Hexadecyl *m*-aminobenzoate	*o*-Cresol	63	53	60°
XIX	do.	α-Naphthol	77	55	60°
XX	Hexadecyl *p*-aminobenzoate	*o*-Cresol	45	44	50°
XXI	*p*-Hexadecyloxyaniline	do.	37	36	90°
XXII	do.	α-Naphthol	47	38	90°

* Extrapolated value.

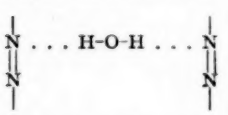
members of the series are shown in Fig. 4, which is drawn to scale from the molecular models.*

The probable angles of orientation given in the last column of the table have all been measured from models; they represent the angle to the water surface of the axis joining the two benzene nuclei on either side of the azo-group (see Fig. 4).

The following observations are made from a survey of the results.

The hydroxy-group attempts to penetrate the water surface as deeply as possible; but in the benzeneazo-β-naphthol series, closest packing is achieved when this group points upwards as shown in Fig. 4(*c*). The azo-group tends to lie below, but close to, the surface. In the compounds having only two benzene nuclei, the azobenzene axis stands vertically to the water surface if the water-attracting groups, *e.g.*, N_2, OH, ·O·, lie along a straight line [Fig. 4(*b*)], but if these groups are not in linear arrangement, the axis is usually tilted in the plane of the nuclei [Fig. 4(*a*)].

The molecules appear to stand about 6 Å apart, measured in a direction at right angles to the plane of the rings. This is consistent with each molecule's being separated from its neighbour by a water molecule, which could join the adjacent azo-groups, as shown in the inset. The compounds with the long-chain alkyl benzoate group in the opposite nucleus to the hydroxy-containing group show evidence of increased tilt due to the water-attraction of the ester group. Thus, the *p*-azobenzoic acid esters are more tilted to the surface than the corresponding ethers or alkylbenzene compounds. The azo-group appears to behave here as a pivot about which the molecular axis may rotate, the strong tendency for the hydroxy-group on one side to plunge



* For simplicity, the positions of the nitrogen atoms only are shown in full; the benzene rings have been drawn through the centres of the carbon atoms. These molecules are actually closest packed when oriented as shown, but because of the omission of the full carbon and hydrogen atoms this is not immediately obvious.

as far as possible beneath the water surface being partly counteracted by the water-attraction of the ester group at the opposite end of the molecule. This explains why the tilt is greater when the ester group is *p*- to the azo-group than when it is in the *m*-position.

In some instances the molecular area found can only be accounted for by assuming that all the molecules do not stand in the same horizontal plane, some being pushed upwards on compression to allow closer packing. This appears to occur with the *p*-hexadecyl derivatives of phenylazophenol and phenylazo-α-naphthol and with the anthranol compound (XVII) in which the bulky anthranol head has to be accommodated under the water surface.

One observation we are unable to account for is that the area occupied by the *p*-alkylphenylazo-β-naphthol compound (VII) is decreased when the ether-oxygen atom comes between the benzene nucleus and the alkyl chain (XIV).

Experimental

The film balance was of Alexander's design (*Nature*, 1947, **159**, 304), with a trough (30 × 25 × 5 cm.) of Pyrex glass, coated with paraffin wax. The scale deflection was 0·125 cm. per dyne. Distilled water was used as substrate. The surface-active compounds were dissolved in an appropriate solvent (usually benzene) and injected below the surface by an " Agla " micrometer syringe. Measurements were made at room temperature and were reproducible to ± 1Å². Stuart-type molecular models were used in determining the orientation data.

Samples of *p*-dodecylaniline, hexadecyl *m*-aminobenzoate, and *p*-hexadecyloxyaniline were supplied by Imperial Chemical Industries Limited, Dyestuffs Division, and were recrystallised from ethanol before use.

Micro-analyses were by Drs. Weiler and Strauss, Oxford, and Dr. A. C. Syme, Royal Technical College, Glasgow. M. p.s are uncorrected.

p-*Dodecylazobenzene* (I).—This was prepared by Mills's method (*J.*, 1895, **67**, 925) for azobenzene. Nitrosobenzene (10·9 g.) was dissolved in glacial acetic acid (30 c.c.) and then added to *p*-dodecylaniline (13·1 g.) dissolved in the minimum volume of glacial acetic acid. The mixture was kept for several days, with occasional shaking; red crystals of the *azo*-compound separated, having m. p. 72° (from acetic acid) (Found: C, 82·0; H, 9·5; N, 7·9. $C_{24}H_{34}N_2$ requires C, 82·3; H, 9·7; N, 8·0%).

4-*Hexadecyloxyazobenzene* (II).—Benzeneazophenol (2 g.) was dissolved in ethanol (40 c.c.) and refluxed for several hours with hexadecyl iodide (4·1 g.) and sodium (0·27 g.). The *ether* separated, after concentration, as yellow prisms (from benzene) (Found: C, 79·5; H, 9·7; N, 6·8. $C_{28}H_{42}ON_2$ requires C, 79·8; H, 10·0; N, 6·7%).

4'-*Hexadecyloxybis(phenylazo)benzene* (III).—*p*-Aminoazobenzene (1 g.) was diazotised and coupled with phenol (0·48 g.) in dilute aqueous sodium hydroxide. Next morning, the precipitated bisazo-compound was recrystallised from ethanol (orange prisms, m. p. 184°) and refluxed (6 hours) with hexadecyl iodide (1·17 g.) and sodium (0·026 g.) in ethanol. The *ether* was separated by filtration and concentration, and formed orange prisms (from benzene) (Found: C, 77·6; H, 8·9; N, 10·4. $C_{34}H_{46}ON_4$ requires C, 77·8; H, 8·8; N, 10·6%).

Hexadecyl p-*Aminobenzoate.*—*p*-Nitrobenzoyl chloride (9·3 g.) and hexadecyl alcohol (12 g.) were refluxed for 6 hours in dry toluene (40 c.c.), and the solvent was then removed by distillation under reduced pressure. The crude hexadecyl *p*-nitrobenzoate (16 g.) was reduced by refluxing it for 12 hours with ethanol (100 c.c.), concentrated hydrochloric acid (0·6 ml.), water (3 c.c.), and iron dust (15 g.). The product was separated by filtration followed by dilution with water.

Diazotisation.—(i) p-*Dodecylaniline and* p-*hexadecylaniline.* A mixture of the base (0·05 mol.), concentrated hydrochloric acid (16 c.c.), and water (150 c.c.) was stirred for 15 minutes at 50°, then cooled to 0°, and sodium nitrite (3·5 g.), in a little water, slowly stirred in. The suspended hydrochloride dissolved to give a yellowish diazo-solution, which was filtered and used for coupling.

(ii) *Hexadecyl* m- *and* p-*aminobenzoates and* p-*hexadecyloxyaniline.* The amino-compound (0·4 mol.) was well ground with water (15 c.c.) and concentrated hydrochloric acid (6·25 c.c.), and the mixture added to water (45 c.c.). 2N-Sodium nitrite solution (12·5 c.c.) was slowly added. Diazotisation was complete after 30 minutes. The esters were diazotised at 5—10°, and the ether at 15—20°.

1-*Hydroxyanthracene.*—The mixture of anthracene-1- and -2-sulphonic acids, obtained by treating anthracene (50 g.) dissolved in glacial acetic acid (100 c.c.) with 20% oleum (65 g.) at

95° for 5 hours (Battegay and Brandt, *Bull. Soc. chim.*, 1923, **33**, 1667), was separated by fractional crystallisation of the sodium salts from hot water.

p-*Hexadecylaniline*.—Hexadecyl alcohol (1 mol.), aniline (1 mol.), aniline hydrochloride (0·3 mol.), and zinc chloride (0·66 mol.) were heated together at 270° for 10 hours, while the water formed was allowed to distil off, and thereafter for a further 12 hours (Coffey, Haddock, and I.C.I. Ltd., B.P. 468 226). The product, a zinc chloride double salt, was cooled, broken up, and heated for 4 hours with 50% aqueous sodium hydroxide. The oil thus formed was dissolved in ether, washed with dilute hydrochloric acid, then with water, and dried ($CaCl_2$). After the ether had been distilled off, the dry oil was distilled *in vacuo*; it had b. p. 240°/11 mm.

p-*Hexadecyl- and* p-*Octadecyl-phenol*.—Hexadecanoyl or octadecanoyl chloride (0·1 mol.) was refluxed for 5 hours with anisole (0·1 mol.). The ketones thus obtained were subjected to Clemmensen reduction and then demethylated by boiling these products for 24 hours with hydriodic acid (8 mols.); the yield was 25%.

3-*Hydroxyphenanthrene*.—Phenanthrene (50 g.), recrystallised from ethanol, was stirred into concentrated sulphuric acid (32·7 c.c.), the temperature then being raised to 120—125° and kept thereat for 4 hours. The mixture was then cooled to room temperature and carefully stirred into a large volume of cold water. Excess of sodium hydroxide was then added; phenanthrene-2- and -3-sulphonates were slowly precipitated and were separated by the difference in solubility of the barium salts (Fieser, *J. Amer. Chem. Soc.*, 1929, **51**, 2460); the 3-sulphonate was then converted into 3-hydroxyphenanthrene by alkali fusion (Smith, *J.*, 1916, **109**, 568); this formed colourless crystals (from ligroin), m. p. 118—119°.

Azo-compounds from Alkylaniline Derivatives.—These were prepared by slowly stirring the diazonium salt solution, previously neutralised with sodium acetate, into a solution of the calculated quantity of the phenol in ice-cold dilute aqueous sodium hydroxide; the azo-compounds were crystallised from the solvents stated and dried. The *p*-isomers were recrystallised several times to ensure complete removal of any *o*-isomers (checked by chromatography on alumina).

Azo-compounds from Long-chain Alkylphenols.—*p*-Hexadecyl- and *p*-octadecyl-phenol were dissolved in alcoholic sodium hydroxide, for coupling.

Azo-compounds from Hexadecyl m- *and* p-*Aminobenzoates and* p-*Hexadecyloxyaniline*.—The diazo-compounds were coupled with *o*- or *p*-cresol or β-naphthol in aqueous sodium hydroxide solution. To couple diazotised hexadecyl *m*-aminobenzoate with α-naphthol, the latter was dissolved in 75% aqueous ethanol and added carefully to the diazo-solution.

p-*Dodecylaniline* ⟶ p-*cresol* (IV). Owing to the low m. p., some difficulty was experienced in crystallising this *compound*, which, when warmed with acetic acid, tended to form oily globules. These were removed by settling and decantation and by charcoal treatment, to enable the dissolved portion to be crystallised; it gave small orange needles, m. p. *ca.* 35—40° (Found: C, 79·0; H, 9·2; N, 7·1. $C_{25}H_{36}ON_2$ requires C, 78·9; H, 9·5; N, 7·4%).

p-*Dodecylaniline* ⟶ β-*naphthol* (V) formed scarlet needles (from ethanol), m. p. *ca.* 75° (Found: C, 80·5; H, 8·5; N, 6·6. $C_{28}H_{36}ON_2$ requires C, 80·8; H, 8·7; N, 6·7%). p-*Dodecylaniline* ⟶ 3-*hydroxyphenanthrene* (VI) formed crimson needles (from ethanol), m. p. 74° (Found: C, 82·2; H, 8·1; N, 6·0. $C_{32}H_{38}ON_2$ requires C, 82·4; H, 8·15; N, 6·0%). p-*Hexadecylaniline* ⟶ β-*naphthol* (VII) was obtained as orange-red prisms (from glacial acetic acid), m. p. 97—98° (Found: C, 81·1; H, 9·2; N, 6·2. $C_{32}H_{44}ON_2$ requires C, 81·1; H, 9·3; N, 5·95%), and *aniline* ⟶ p-*hexadecylphenol* (VIII) as orange-yellow prisms (from glacial acetic acid and then ethanol), m. p. 84° (Found: N, 6·5. $C_{28}H_{42}ON_2$ requires N, 6·65%). *Aniline* ⟶ p-*octadecylphenol* (IX) formed orange-yellow prisms (from glacial acetic acid and then ethanol), m. p. 87° (Found: C, 80·1; H, 10·1; N, 6·4. $C_{30}H_{46}ON_2$ requires C, 80·0; H, 10·2; N, 6·25%), and *hexadecyl* m-*aminobenzoate* ⟶ p-*cresol* (X) orange prisms (from ethanol), m. p. 82° (Found: C, 74·8; H, 9·1; N, 5·9. $C_{30}H_{44}O_3N_2$ requires C, 75·0; H, 9·2; N, 5·9%). *Hexadecyl* m-*aminobenzoate* ⟶ β-*naphthol* (XI), orange prisms, m. p. 84° (Found: C, 77·0; H, 8·9; N, 5·11. $C_{39}H_{44}O_3N_2$ requires C, 76·8; H, 8·5; N, 5·4%), and the p-*amino*-analogue (XII), orange-red prisms, m. p. 80°. (Found: C, 76·5; H, 8·7; N, 5·6%), were both crystallised from ethanol. p-*Hexadecyloxyaniline* ⟶ p-*cresol* (XIII) formed yellowish-orange needles (from glacial acetic acid and then ethanol), m. p. 67° (Found: C, 77·2; H, 9·8; N, 6·5. $C_{29}H_{44}O_2N_2$ requires C, 77·0; H, 9·75; N, 6·2%), and the β-*naphthol* analogue (XIV) formed dark red prisms (from ethanol), m. p. indef. (Found: C, 78·5; H, 9·1; N, 5·5. $C_{32}H_{44}O_2N_2$ requires C, 78·7; H, 9·0; N, 5·7%). p-*Dodecylaniline* ⟶ o-*cresol* (XV), orange prisms, m. p. 48° (Found: C, 79·0; H, 9·9; N, 7·3. $C_{25}H_{36}O_2N_2$ requires C, 78·9; H, 9·5; N, 7·4%), and its α-*naphthol* analogue (XVI), dark red prisms, m. p. 120° (Found: C, 80·7; H, 8·4; N, 6·5. $C_{28}H_{36}ON_2$ requires C,

80·8; H, 8·7; N, 6·7%), were both crystallised from ethanol. The 1-*hydroxyanthracene* analogue (XVII) formed bluish-red prisms (from glacial acetic acid), m. p. 60° (Found: C, 82·1; H, 8·4; N, 5·9. $C_{32}H_{38}ON_2$ requires C, 82·4; H, 8·2; N, 6·0%). *Hexadecyl* m-*aminobenzoate* ⟶ o-*cresol* (XVIII) formed orange-yellow prisms (from glacial acetic acid), m. p. 103° (Found: C, 74·7; H, 9·1; N, 6·1. $C_{30}H_{44}O_3N_2$ requires C, 75·0; H, 9·2; N, 5·9%), and its α-*naphthol* analogue (XIX), crystallised from ethanol, then purified by alumina chromatography from benzene solution containing 0·5% of ethanol, and finally crystallised from ethanol, formed dark red prisms, m. p. 90° (Found: C, 76·6; H, 8·3; N, 5·6. $C_{33}H_{44}O_2N_2$ requires C, 76·8; H, 8·55; N, 5·4%). *Hexadecyl* p-*aminobenzoate* ⟶ o-*cresol* (XX) crystallised in orange prisms (from glacial acetic acid), m. p. 96° (Found: C, 74·8; H, 9·5; N, 6·0. $C_{30}H_{44}O_3N_2$ requires C, 75·0; H, 9·2; N, 5·9%). p-*Hexadecyloxyaniline* ⟶ o-*cresol* (XXI) formed orange prisms (from glacial acetic acid), m. p. 58° (Found: C, 76·7; H, 10·0; N, 6·1. $C_{29}H_{44}O_2N_2$ requires C, 77·0; H, 9·75; N, 6·2%), and the α-*naphthol* analogue (XXII), purified as (XIX), dark red prisms, m. p. 108° (Found: C, 78·6; H, 8·8; N, 5·6. $C_{32}H_{44}O_2N_2$ requires C, 78·7; H, 9·05; N, 5·75%).

One of us (E. L. N.) thanks the Directors of Imperial Chemical Industries Ltd., Dyestuffs Division, for financial assistance. A number of intermediates, in addition to those already mentioned, were supplied by the same firm. We are also indebted to the Chemical Society for a research grant to assist in later stages of the work. Thanks are due to Mr. P. M. Yacoubian for carrying out some of the initial experiments, and to Professor J. W. Cook, F.R.S., for a reference sample of 3-hydroxyphenanthrene.

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Royal Technical College, Glasgow, C.1. [*Received, October 10th*, 1951.]

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167. *Amorphous Carbon.*

By Thomas D. Smith.

Carbons, prepared by carbonisation of organic compounds, have been examined by *X*-ray diffraction and gas adsorption. The presence of oxygen in the organic molecule profoundly affects the crystallographic character of the resultant chars. Surface areas of these chars vary appreciably: very large areas may be due to the presence of a highly porous three-dimensional cross-linked structure; small areas occur when the material decomposes in the fused state.

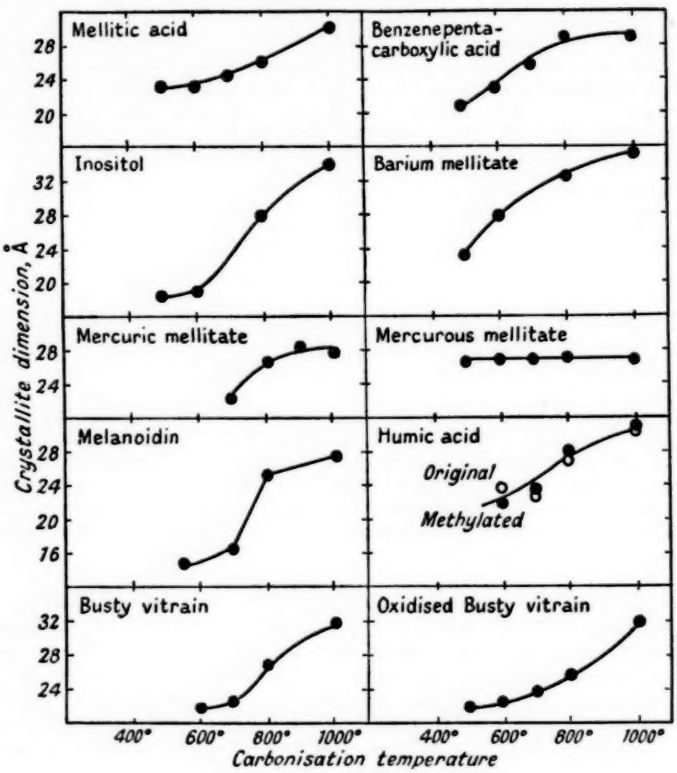
It has been suggested (Riley, *Quart. Reviews*, 1947, I, 59) that amorphous carbons are built up of two types of structure, *viz.*, (1) a turbostratic, lamellar, graphite-like structure, and (2) a disordered, three-dimensional cross-linked structure. The latter has been described as a three-dimensional repetition of *o*-tetraphenylene residues. The evidence for this view has been assembled from detailed *X*-ray examination of a large number of amorphous carbons prepared from a variety of organic substances (Blayden, Gibson, and Riley, "Ultra-Fine Structure of Coals and Cokes," B.C.U.R.A., London, 1947, 178; *J. Inst. Fuel*, 1945, War Time Bulletin, 117; Gibson, Holohan, and Riley, *J.*, 1946, 456). The method of examination consists in measuring the half-peak widths of the diffraction bands and calculating from these the dimensions of the average, hypothetical, cylindrical crystallites. It is thus possible to follow the growth of the crystallites with increasing temperature of carbonisation. The average height (*c* dimension) of the crystallites is calculated from the corrected half-peak width of the 002 diffraction halo by means of Jones's formula $\beta = 1{\cdot}0\lambda/L_c \cos\theta$; the average diameter (*a* dimension) is calculated from the half-peak width of the 10 cross-lattice diffraction halo by Warren's formula $\beta = 1{\cdot}84\lambda/L_a \cos\theta$.

These studies have been extended to a series of amorphous carbons prepared by carbonisation of organic compounds of high oxygen content. The surface areas have been determined by adsorption of nitrogen. The following materials were carbonised at 5° per minute in an atmosphere of nitrogen, up to various temperatures: mellitic acid,

barium mellitate, mercuric and mercurous mellitate, inositol, benzenepentacarboxylic acid, quinol humic acid, methylated humic acid, melanoidin, and oxidised Busty vitrain. Figs. 1 and 2 summarise the results of the crystallite-growth studies.

Although the individual characteristics, molecular sizes, and shapes of the original materials differed considerably, all the chars exhibited almost constant c dimensions; the a dimensions in general showed a growth from about 20 Å at 400° to about 32 Å at 1000°. The behaviour of the c dimensions is in striking contrast to that exhibited by chars obtained by carbonising materials of low oxygen content (*e.g.*, dibenzanthrone, pitch extract, bituminous coal), but is similar to the behaviour of the cellulose chars previously studied. It is significant that none of the chars contained less than 4% of oxygen (by difference).

FIG. 1. *"a" Dimensions.*



The pitches, peat, dibenzanthrone etc., yield chars having a turbostratic structure which is mobile in that growth can take place along the c axis. On the other hand, cellulose and the materials listed in Figs. 1 and 2 yield chars having, even at low temperatures, a rigid structure. The presence of oxygen apparently inhibits growth along the c axis. Constant c dimensions were obtained whether the oxygen-containing compounds decomposed in the solid state (as in the case of humic acid, mellitic acid, and mellitates), or in the fused state (inositol and benzenepentacarboxylic acid).

The mechanism by which oxygen causes rigidity in carbon crystallites is obscure but is possibly due to some form of cross-linking between the lamellar planes. Oxidation of a Busty vitrain for 100 days at 150° appeared to convert a turbostratic lattice into a system of rigid carbon crystallites (Fig. 2). The c dimensions of the chars from methylated

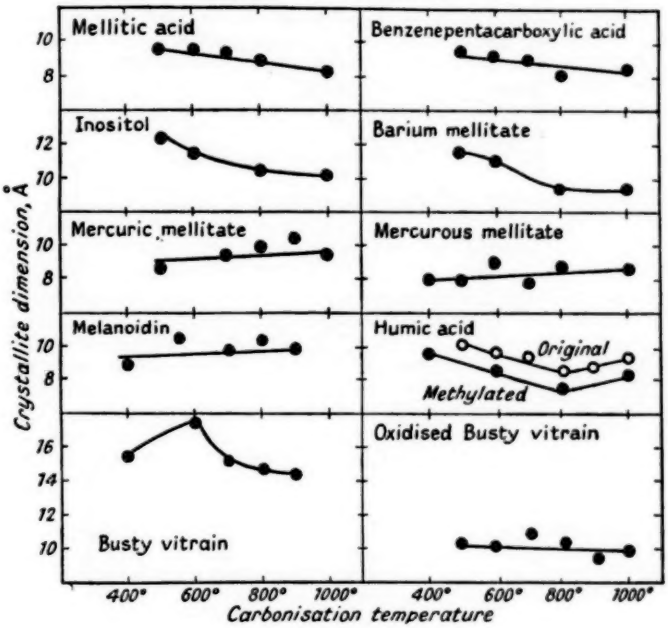
humic acid were consistently about 1 Å less than those from the original material. This difference, although small, may indicate that introduction of the methoxyl groups caused an increase in the disordering of the crystallites.

The surface structure of the carbons was examined by adsorption of nitrogen at the temperature of liquid nitrogen. Sigmoidal (type 2) isotherms were obtained in every case. The total surface areas of the carbons were calculated by the Brunauer–Emmett–Teller equation:

$$V = \frac{V_m CX\,[1 - (n+1)X^n + nX^{n+1}]}{(1-X)[1 + (C-1)X - CX^{n-1}]}$$

where V_m is the volume of gas adsorbed at N.T.P. when the surface is covered by a monolayer, V the volume adsorbed at pressure p, X the relative pressure, n the number of

FIG. 2. *"c" Dimensions.*



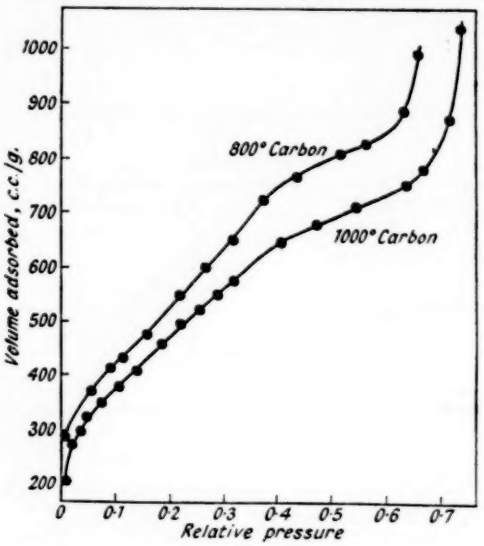
layers to which the gas is limited, and C is a constant dependent on the heat of adsorption.

The simple limiting form of the B.–E.–T. equation did not give linear graphs owing to the small value of n. Similarly, the Harkins–Jura equation did not apply (Smith and Bell, *Nature*, 1948, **162**, 109). Joyner, Weinberger, and Montgomery's method (*J. Amer. Chem. Soc.*, 1945, **67**, 2182) was used to derive the value of V_m; 16·2 sq. Å was taken as the area of surface covered by one molecule of adsorbate.

The values of V_m, n, and specific surface area are given in the Table. The high surface area of the barium mellitate chars might have been expected, as it is well known that when carbonaceous materials are carbonised with inorganic salts an increase in the surface area is obtained. However, surfaces of this magnitude, particularly those occurring in hexachlorobenzene carbons, can hardly be accounted for by the prismatic and basal surfaces of minute graphite crystallites; they indicate intracrystalline penetration of the adsorbate. This lends additional weight to the cross-linked aromatic structure suggested by Gibson, Holohan, and Riley, which possesses a highly developed pore structure. The isotherms of the hexachlorobenzene carbons show a slight but distinct tendency to flatten out at about

0·5 relative pressure (Fig. 3). More definite plateaux, but of the same nature, were obtained by Zettlemoyer and Walker (*Ind. Eng. Chem.*, 1947, **39**, 69) in a study of active magnesia. Such isotherms probably indicate that two types of adsorbing surface are present, one existing as pores of fairly uniform diameter, the other as pores having a random size distribution.

FIG. 3. *Adsorption isotherms on carbons from hexachlorobenzene.*



Surface areas from the B.–E.–T. *equation.*

Sample	Carbonisation temp.	V_m, c.c./g.	n	Specific surface area, sq. m./g.
Mellitic acid	500°	153	1·4	670
	1000	147	1·3	640
Inositol	500	50	4·0	218
	600	86	3·6	375
	1000	15	9·0	65
Barium mellitate	600	153	2·7	665
	800	379	3·0	1650
	1000	312	2·7	1355
Mercuric mellitate	800	110	1·8	480
Mercurous mellitate	800	179	1·9	780
Benzenepentacarboxylic acid	1000	3·7	3·2	16
Hexachlorobenzene	800	488	5·5	2125
	1000	425	4·0	1850
Cellulose	1000	1·5	3·0	66·5
Melanoidin	800	1·9	2·3	8

The very low surface area of the benzenepentacarboxylic acid chars was probably due to the charring's having occurred in a fused state. A shiny, highly swollen coke was produced. The formation of a carbon under these conditions must tend to inhibit the production of an inner surface.

EXPERIMENTAL

Mellitic acid was prepared by Juettner's method (*J. Amer. Chem. Soc.*, 1937, **59**, 208). 200 G. of high-temperature coke, on oxidation with fuming nitric acid (3 l.) containing ammonium vanadate (0·5 g.), followed by alkaline permanganate, gave after electrodialysis (2—3 amp.; 66 hours) a white, crystalline ammonium salt, which did not contain any oxalic

acid. The free acid was obtained by electrodialysis (Found : C, 42·1; H, 1·8. Calc. for $C_{12}H_6O_{12}$: C, 42·1; H, 1·75%).

The acid (m. p. 283—286°, decomp.) was identified by esterifying it with diazomethane and recrystallising of the hexamethyl ester from methyl alcohol; m. p. 87.

Benzenepentacarboxylic acid (B.D.H.) was purified by recrystallisation from absolute ethyl alcohol.

Barium mellitate was prepared by addition of an aqueous solution of " AnalaR " barium chloride in slight excess to an aqueous solution of ammonium mellitate. The dense, white, flocculent precipitate was thoroughly washed with hot water and dried at 105°. Under the microscope it was seen to consist of minute, acicular crystals (Found : C, 17·6; Ba, 51·2; H_2O, 6·8. Calc. for $C_{12}O_{12}Ba_3,3H_2O$: C, 18·0; Ba, 51·4; H_2O, 6·7%). This salt was carbonised in the standard way, and the chars were thoroughly extracted with boiling hydrochloric acid.

Mercurous mellitate was prepared by adding an excess of mercurous nitrate, dissolved in very dilute nitric acid, to a hot solution of mellitic acid. The white precipitate, which coagulated on stirring, was filtered off, washed thoroughly, and dried at 110° (Found : Hg, 73·1. Calc. for $C_{12}O_{12}Hg_6,6H_2O$: Hg, 73·1%). On carbonisation it yielded a carbon in which mercury could not be detected; a considerable amount of mercury condensed on the cooler parts of the furnace tube, doubtless owing to decomposition of the oxides.

Mercuric mellitate was prepared by adding hot mercuric chloride solution to a hot solution of ammonium mellitate. A heavy white precipitate was produced which was filtered off, thoroughly washed, and dried at 140° (Found : Hg, 57·3. Calc. for $C_{12}O_{12}Hg_3,6H_2O$: Hg, 57·5%). On carbonisation in nitrogen, as with the mercurous salt, it afforded globules of mercury in the cool regions of the furnace tube leaving chars containing no detectable quantity of mercury.

Quinol humic acid was prepared by alkaline persulphate by Eller and Koch's method (*Ber.*, 1920, **53**, 1469) (Found : C, 57·55; H, 3·1. Calc. for $C_6H_4O_3$: C, 58·05; H, 3·25%). It was methylated five times by suspending it in dioxan and treating it with an ethereal solution of diazomethane, the methoxyl content rising to 7·1%.

Melanoidin complex was prepared by heating an aqueous solution of dextrose (6 g.) with glycine (15 g.) for 2 hours. The solution became dark brown. On evaporation, a brittle, brown solid remained (4·6 g.).

Hexachlorobenzene carbon was produced by the method of Gibson, Holohan, and Riley (*J.*, 1946, 461), and heated in nitrogen to various temperatures in the usual way.

The isotherms were determined by adsorption of nitrogen at liquid-nitrogen temperature in an apparatus of similar design to that of Brunauer and Emmett (*J. Amer. Chem. Soc.*, 1934, **56**, 35; 1937, **59**, 1553) as modified by Harkins and Jura (*ibid.*, 1944, **66**, 1366). All samples of carbon were degassed at 200° for 4 hours under a very high vacuum.

The foregoing investigation was part of the fundamental research programme of the British Coke Research Association, and the author thanks Mr. H. E. Blayden, Dr. J. Gibson, and Dr. H. L. Riley for advice and encouragement.

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168. *Pernitrous Acid. The Reaction between Hydrogen Peroxide and Nitrous Acid, and the Properties of an Intermediate Product.*

By E. Halfpenny and P. L. Robinson.

The rate of the reaction between hydrogen peroxide and nitrous acid, at low acidities, is shown to be proportional to the concentrations of hydrogen peroxide, nitrous acid, and hydrogen ion. This reaction, and the reactions of nitric oxide and nitrogen dioxide with hydrogen peroxide, are shown to produce pernitrous acid. A product of all the reactions, believed to be the pernitrous acid, initiates the polymerisation of methyl acrylate and also hydroxylates and nitrates benzene. To explain these observations a free-radical mechanism is proposed in which it is suggested that pernitrous acid undergoes homolytic fission to give hydroxyl radicals and nitrogen dioxide.

Despite a considerable literature, the nature and, in a measure, the properties of the peroxy-compounds of nitrogen remained uncertain. Of the two per-acids more definitely postulated, the more clearly defined was pernitrous acid; the other, pernitric acid, has been described as resulting from admixture of concentrated hydrogen peroxide and nitrogen pentoxide (Schwarz, *Z. anorg. Chem.*, 1948, **256**, 1) or by bombardment of nitric acid with fast electrons (Allen, *J. Phys. Coll. Chem.*, 1948, **52**, 479). The deduction that it is HNO_4, admittedly reasonable, does not appear to be supported by quantitative evidence. Earlier writers did not distinguish between the per-compounds; and many observations, attributed to reactions of pernitric, actually refer to pernitrous acid.

From the interaction of alkyl nitrites and ethyl hydroperoxide, Baeyer and Villiger (*Ber.*, 1901, **34**, 755) inferred that the reaction between hydrogen peroxide and nitrous acid involved the formation of an unstable pernitrous acid. In 1904, Raschig (*Z. angew. Chem.*, 1904, **17**, 1419; *Ber.*, 1907, **40**, 4585) showed that a mixture of hydrogen peroxide and nitrous acid is a stronger oxidising agent than either of its components but ascribed the fact to the presence of pernitric acid, formulated as HNO_4. However, the oxidising properties of the mixture led Schmidlin and Massini (*Ber.*, 1910, **43**, 1170) to call the new substance a hydroperoxide of nitrous acid, HO·ONO, not pernitric acid. Trifonow (*Z. anorg. Chem.*, 1922, **124**, 123, 136) and Pollak (*ibid.*, 1925, **143**, 143) attempted to establish the formula of the per-acid by observing the hydrogen peroxide : nitrous acid ratio which gave the maximum liberation of bromine from hydrobromic acid. Pollak found no recognisable stoicheiometric relation between the reactants but Trifonow's measurements led him to call the initial product dinitryl peroxide, N_2O_6, which he believed was rapidly hydrolysed by water to pernitric acid. In this paper, Trifonow mentioned the transient yellow colour assumed by the mixture (in the absence of hydrobromic acid) : this he attributed to the release of nitrogen dioxide in the solution.

In 1929, Gleu and Roell (*ibid.*, **179**, 233) showed that the oxidation of aqueous sodium azide by ozone produced a relatively persistent yellow colour and described it as due to sodium pernitrite. This they were unable to isolate, but, from an analysis of the solution, they formulated it as $NaNO_2O$. Six years later Gleu and Hubold (*ibid.*, **223**, 305) concluded from the analysis of a similar yellow solution, prepared by mixing acidified hydrogen peroxide with sodium nitrite and immediately making the whole alkaline with sodium hydroxide, that they were dealing with the same compound. Kortum and Finckh (*Z. physikal. Chem.*, 1941, *B*, **48**, 32), showed that the yellow solutions had an ultra-violet absorption band with a maximum close to that of the nitrate ion, but about fifteen times more intense and much broader.

In face of the above evidence, and after many of the conclusions described in this communication had been reached, Abel (*Monatsh.*, 1949, **80**, 449) denied the existence of pernitrous acid and ascribed the colour observed in acid solution to nitrogen dioxide. He criticised the formula, $HNO_2{\cdot}O$, on the grounds that Gleu and Hubold's experimental results indicate a ratio of one gram-equivalent (not one gram-atom) of active oxygen to

one mole of nitrous acid, which would correspond to $(HNO_2)_2O$. It appears to us that Abel's criticism may have arisen from the fact that Gleu and Hubold used the oxidation–reduction equivalent of nitrous acid, *i.e.*, one-half of the molecular weight, when tabulating their results. If this is taken into consideration their deduction is correct and, furthermore, is substantiated by Rius and Foz (*Anal. Fis Quím.*, 1940, **36**, 308) whose analysis of the yellow solution by a potentiometric method gave identical results.

The present work aimed at securing further information about the reaction between hydrogen peroxide and nitrous acid. It has been possible to examine some of its kinetic features in solutions of very low acidity over a limited concentration range. The general rate expression obtained does not appear to correspond with that in a paper (which we have only seen in abstract) by Schilow, Rybakow, and Pal (*Bull. Inst. Polytechn. Ivanovo-Vosniesinsk*, 1930, **15**, 85; *Chem. Zentr.*, 1931, II, 377). The frequently contradictory previous evidence has led us to repeat some of the earlier work. The formation of the unstable yellow intermediate in the reaction in acid solution was at once confirmed, and by devising a flow method using alternately a tube and a channel its properties have been more precisely observed. In particular it has been unequivocally shown to be the precursor of the very much more stable yellow alkaline solution which Gleu and his co-workers claimed to contain sodium pernitrite, NaO·ONO. This claim being admitted, the yellow unstable intermediate would appear to be pernitrous acid, HO·ONO.

Experiments are now described which appear to invalidate the arguments of those who have sought to establish the formula of the per-acid by observing the liberation of bromine from hydrobromic acid. We have found that the short lived pernitrous acid appears in the oxidation, severally, of nitric oxide and nitrogen dioxide with hydrogen peroxide: both reactions seem to involve, as a preliminary step, the formation of nitrous acid.

Our polymerisation experiments show that mixing acidified hydrogen peroxide and a nitrite produces free radicals. But the acidification of sodium pernitrite has also been shown to cause the polymerisation of methyl acrylate; whence we argue that the free radicals are not produced during the formation of the pernitrous acid, but appear in the course of its decomposition.

Trifonow (*loc. cit.*) had previously observed that, if benzene is present when pernitrous acid is formed, both benzene and the aqueous solution become yellow, which, owing to a darkening induced by alkali, he ascribed to the formation of phenols. We have now isolated these phenols and relate their presence and the polymerisation of methyl acrylate to the liberation of hydroxyl radicals. In addition to the phenols formed from benzene in these circumstances, we find, remarkably, an appreciable amount of nitrobenzene. This new process of nitration applicable to hydrocarbons and other compounds is of especial interest in that it takes place at the ordinary temperature and in an aqueous media of low acidity. Its investigation is described by the authors in the succeeding paper.

Experimental

Kinetic features of the reaction between hydrogen peroxide and nitrites.

Under neutral conditions hydrogen peroxide and sodium nitrite do not react, but on acidification with a mineral acid reaction is immediate and extremely fast. Indeed, acidified hydrogen peroxide can be titrated with sodium nitrite solution, titanium sulphate being used as an internal indicator responding to hydrogen peroxide. When 1% sodium nitrite is added to dilute acidified hydrogen peroxide, the indicator becomes colourless when the molecular ratio $NaNO_2 : H_2O_2$ equals 1 : 1·05. Should, however, hydrogen peroxide be added to acidified sodium nitrite, the indicator develops colour when the ratio of 1 : 0·99 is reached, the smaller peroxide requirement being probably due to loss of nitrous acid. These results suggest the, presumably rapid, reaction

$$H_2O_2 + HNO_2 \longrightarrow HNO_3 + H_2O \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad (1)$$

We found that, when excess of hydrogen peroxide was used and back-titrated with potassium permanganate, the ratio nitrite : peroxide depended on addition of the hydrogen peroxide; when addition is dropwise, the ratio is 1 : 0·96, but when very rapid 1 : 0·85.

On changing from excess of mineral acid to a concentration giving a pH of *ca.* 4, we got measurable reaction rates. These were ascertained by decomposing the residual hydrogen peroxide, after known intervals, with manganese dioxide, and measuring the oxygen evolved,

FIG. 1.

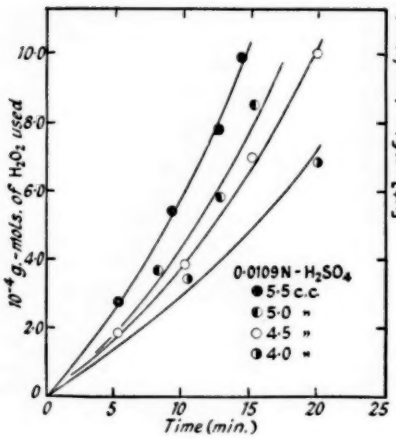


FIG. 2.

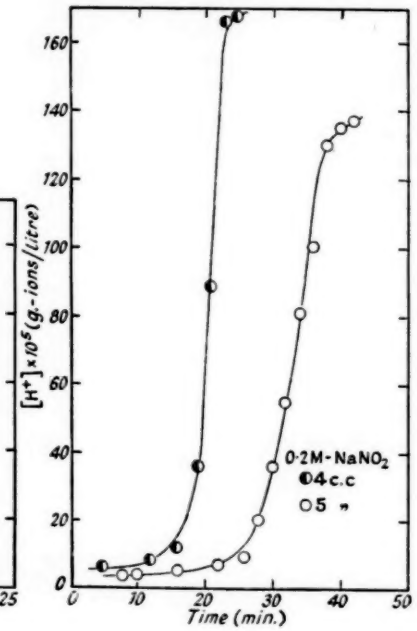


FIG. 3.

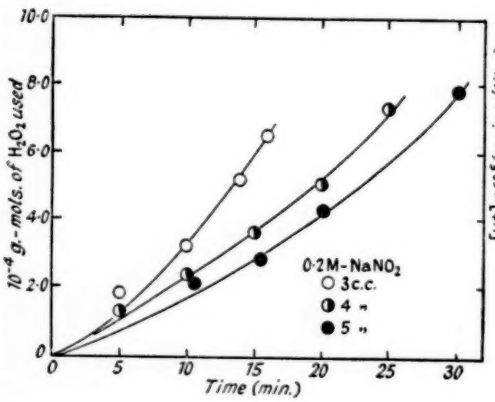
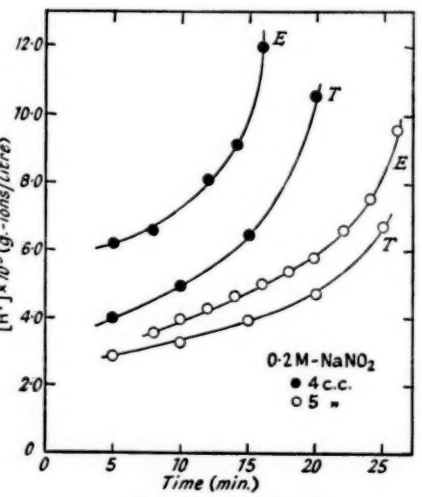


FIG. 4.



in a gas burette. Fairly consistent results were obtained, and, as a useful check, when the reaction was allowed to run its full course, the ratio proved to be 1 : 1, in conformation with equation (1). Measurements were made in solutions containing 5 c.c. of 0·2M-sodium nitrite, 10 c.c. of 1% hydrogen peroxide and, respectively, 5·5, 5·0, 4·5, and 4·0 c.c. of 0·0109N-

sulphuric acid in a total volume of 35 c.c. The amounts of hydrogen peroxide used are expressed graphically in Fig. 1.

The rate of consumption of hydrogen peroxide increased rapidly with time, which is understandable if hydrogen-ion concentration governs the speed, since the pH decreases in the course of the reaction. This is because, the added mineral acid being insufficient to convert all the nitrite into nitrous acid, the hydrogen-ion concentration is due entirely to the dissociation of nitrous acid, which is itself reduced by the common-ion effect of the excess of nitrite; but, as the reaction proceeds, the excess of nitrite is oxidised to nitrate with a consequential increase in hydrogen-ion concentration through reduction in the common-ion effect. Measurements of pH with a glass electrode during the reactions of solutions containing 5 c.c. of 0·0109N-sulphuric acid, 5 c.c. of 0·36M-hydrogen peroxide, 4 and 5 c.c. of 0·2M-sodium nitrite, in a total volume of 35 c.c., plotted against time in Fig. 2, show that the hydrogen-ion concentration actually does increase rapidly in the course of the reaction.

Rates of reaction in these two systems, and in another containing 3 c.c. of 0·2M-sodium nitrite, are plotted in Fig. 3. The rate is greater in solutions with less nitrite, probably because the reactant is nitrous acid; the nitrite ion as such reduces the rate by lowering the hydrogen-ion concentration.

From the rate curves for 4 and 5 c.c. of nitrite (Fig. 3) the hydrogen-ion concentration after certain times can be calculated, on the assumption that it is due to nitrous acid the dissociation of which is influenced by nitrite ion. These for the early stages of the reaction are plotted, along with the experimentally measured values, in Fig. 4. The calculated values are lower than the observed, possibly because the value of K_a available was for 12·5° and the actual temperature was 19°; but they are sufficiently close to support the view advanced. The difference in the initial rates, evident in Fig. 3, must be due to differences in initial concentrations of nitrite ion and/or of hydrogen ion since the initial concentration of hydrogen peroxide was constant and that of nitrous acid almost constant.

$$\begin{aligned} \text{Let initial rate} &= K \times [H^+]^x[NO_2^-]^y \\ \text{Since} \quad [H^+] &= K_a[HNO_2]/[NO_2^-] \\ [NO_2^-] &= K'/[H^+] \\ \text{Therefore, initial rate} &= K''[H^+]^x/[H^+]^y = K''[H^+]^{x-y} \end{aligned}$$

The initial rates, obtained from Fig. 3, when plotted against the calculated hydrogen-ion concentration, exhibit a straight line passing through the origin (equation: initial rate = 0·615[H^+]) (see Table 1) and indicate an initial rate directly proportional to the hydrogen-ion

TABLE 1.

0·2M-$NaNO_2$ (c.c.)	$10^5[H^+]$ calc. (M)	10^5 × Initial rate (g.-mol. H_2O_2/min.) (N)	N/M (observed)
3·0	4·6	2·85	0·620
4·0	3·35	2·1	0·627
5·0	2·65	1·6	0·604

(N/M, determined from graph, = 0·615.)

concentration, *i.e.*, $x - y = 1$. In Fig. 1 (H_2O_2 constant) the concentrations of nitrous acid approximate to those of sulphuric acid, and the concentrations of nitrite to the difference between the initial nitrite and the sulphuric acid (*i.e.*, a — H_2SO_4 concn., where a equals initial $NaNO_2$ concn.).

$$\begin{aligned} \text{Let initial rate} &= K[H^+]^x[NO_2^-]^y[HNO_2]^z \\ &= K'[H^+]^{x-y}[HNO_2]^{z+y} \end{aligned}$$

Initial rates, calculated hydrogen-ion concentrations, and nitrous acid concentrations (derived from Fig. 1) are given in Table 2. The initial rate, when plotted against $[H^+][HNO_2]$, gives a straight line passing through the origin {equation: initial rate/($[H^+][HNO_2]$) = 9·4}. Hence, the initial rate = $K[H^+][HNO_2]$ and both $(x - y)$ and $(z + y)$ have the value of unity, whence either $x = 1$, $y = 0$, $z = 1$; or $x = 2$, $y = 1$ and $z = 0$, *i.e.*, (*a*) initial rate = $K[H^+][HNO_2]$, or (*b*) initial rate = $K'[H^+]^2[NO_2^-]$. Owing to the interdependence of $[H^+]$ and $[NO_2^-]$, nitrite cannot be conclusively ruled out as a reactant. But there is no evidence that

TABLE 2.

0·0109N-H_2SO_4 (c.c.)	10^5[H^+], calc. (g.-ions/l.)	10^3[HNO_2] (g.-mol./l.)	10^8[H^+][HNO_2] (*A*)	10^5 Initial rate (g.-mol. H_2O_2/min.) (*B*)	$10^{-3}B/A$ (observed)
5·5	2·93	1·71	5·01	4·8	9·6
5·0	2·65	1·55	4·10	3·8	9·3
4·5	2·36	1·4	3·31	3·0	9·0
4·0	2·1	1·25	2·63	2·6	9·9

($10^{-3}B/A$, determined from graph, = 9·4.)

the nitrite ion reacts as such, and, since the adoption of (*b*) requires the implausible exclusion of [HNO_2] as a rate-determining factor, equation (*a*) which implies that the rate varies directly with both nitrous acid and hydrogen ion is chosen.

FIG. 5.

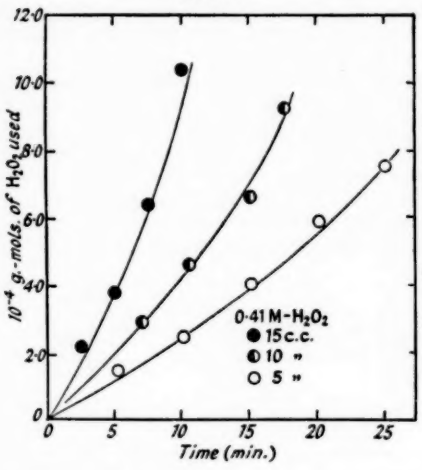
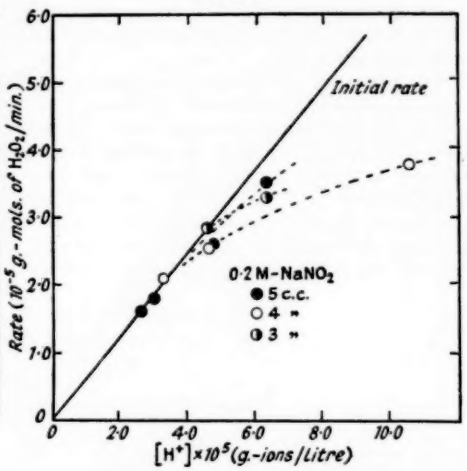


FIG. 6.



The effect of hydrogen peroxide on the reaction rate, shown in Fig. 5, was observed by measuring the amount of available oxygen used after various times in solutions (total volume, 35 c.c.) containing nitrite (5 c.c.; 0·2M.), sulphuric acid (5 c.c.; 0·0109N.) and, severally, 15, 10, and 5 c.c. of hydrogen peroxide (1%). The initial rates (Fig. 5) and the corresponding initial hydrogen peroxide concentrations give a straight-line plot passing through the origin (equation: initial rate/[H_2O_2] = 0·354 $\times$ 10^{-3}) (Table 3) and show that the rate is directly proportional to the concentration of hydrogen peroxide.

TABLE 3.

0·41M-H_2O_2 (c.c.)	[H_2O_2] (g.-mol./l.) (*C*)	10^4 $\times$ Initial rate (g.-mol. H_2O_2/min.) (*D*)	$10^3D/C$ (observed)
15	0·176	0·64	0·363
10	0·117	0·40	0·343
5	0·059	0·22	0·373

($10^3D/C$, determined from graph, = 0·354.)

The foregoing results which deal only with the initial stages of the reaction lead to the following rate equation

$$R = -\mathrm{d}(H_2O_2)/\mathrm{d}t = K[H_2O_2][HNO_2][H^+]$$

Values for K have been calculated using the initial rate (R) and other data:

(i) $R/[H^+] = K[H_2O_2][HNO_2]$
$R/[H^+] = 6{\cdot}15 \times 10^{-1}$ (Table 1); $[H_2O_2] = 5{\cdot}1 \times 10^{-2}$; $[HNO_2] = 1{\cdot}56 \times 10^{-3}$ (Fig. 3)

whence $K = 7{\cdot}73 \times 10^3$.

(ii) $R/[H_2O_2] = K[H^+][HNO_2]$
$R/[H_2O_2] = 3{\cdot}54 \times 10^{-4}$ (Table 3); $[H^+] = 2{\cdot}66 \times 10^{-5}$; $[HNO_2] = 1{\cdot}56 \times 10^{-3}$ (Fig. 5)

whence $K = 8{\cdot}57 \times 10^3$.

(iii) $R/([HNO_2][H^+]) = K[H_2O_2]$
$R/([HNO_2][H^+]) = 9{\cdot}42 \times 10^2$ (Table 2); $[H_2O_2] = 1{\cdot}06 \times 10^{-1}$ (Fig. 1)

whence $K = 8{\cdot}9 \times 10^3$.

Thus, K (mean) $8{\cdot}4 \times 10^3$ (concn., g.-mol.; time, minutes).

Some of the increase in rate during the reaction is derived from the change in hydrogen-ion concentration. That it comes mainly from this, and little if at all from chain propagation through an intermediate compound, is made evident by plotting (Fig. 6) calculated hydrogen-ion concentrations against measured rates, the former being deduced by the hydrogen peroxide remaining at a given instant and the latter by drawing tangents to the curves in Fig. 3. In all cases the observed rate is less than the rate calculated from the hydrogen-ion concentration (if changes in the concentrations of the other reactants are ignored).

The validity of the rate equation with $K = 8{\cdot}4 \times 10^3$ (see above) has been tested over the limited range studied. Arbitrary points taken on curves in Figs. 1, 3, and 5 have provided values to introduce into the rate equation. Rates so obtained, and the experimental rates derived from the selected points on the curves, may be compared in Table 4 in which they show an agreement, in spite of the approximations involved in arriving at the calculated rate, which

TABLE 4.

Points selected	$10^5[H^+]$ (g.-ion/l.)	$10^3[HNO_2]$ (g.-mol./l.)	$10^2[H_2O_2]$ (g.-mol./l.)	$10^5 \times$ Rate, calc. (g.-mol. H_2O_2/min.)	$10^5 \times$ Rate, observed (g.-mol. H_2O_2/min.)
Fig. 1, 5·5 c.c. H_2SO_4 after 10 min. reaction	7·5	1·72	8·95	9·7	8·2
Fig. 5, 10·0 c.c. H_2O_2 after 13 min. reaction	6·52	1·56	10·10	8·6	6·2
Fig. 3, 4·0 c.c. $NaNO_2$ after 9·5 min. reaction	4·7	1·56	4·55	2·8	2·5
Fig. 5, 5·0 c.c. H_2O_2 after 15 min. reaction	4·6	1·56	4·71	2·8	3·2

augurs well for the correctness of the equation in expressing the course of the reaction within the limited concentration ranges of the reactants, *viz.*, $[H^+]$ 2—$4{\cdot}6 \times 10^{-5}$ g.-ions per l., $[HNO_2]$ 1·2—$1{\cdot}7 \times 10^{-3}$ g.-mol. per l., $[H_2O_2]$ 0·6—$1{\cdot}8 \times 10^{-1}$ g.-mol. per l.

The reaction mixture and bromide ion.

The mixture liberates bromine from hydrobromic acid, the amount rising with an increase in the ratio $HNO_2 : H_2O_2$, up to a maximum, and thereafter falling, because bromine reacts with nitrite, finally to zero. In investigating the stoicheiometry in the presence of hydrobromic acid, several factors have to be taken into account. First, since the reaction between sodium nitrite and hydrogen peroxide in an appreciable acidity is extremely fast, the bromide must be present initially. Secondly, since bromine is liberated from hydrobromic acid by hydrogen peroxide of even moderate strength its concentration must be kept low. Thirdly, since bromine is reduced fairly rapidly by nitrous acid, the nitrite must be added dropwise to acidified hydrogen peroxide–bromide to ensure that the major part of it reacts with the peroxide. Reproducible determinations of bromine could not be made with the " Spekker " photo-absorptiometer owing to the photochemical reaction between bromine and hydrogen peroxide, but concordance resulted from extraction of the bromine with carbon tetrachloride and titration of its equivalent iodine with thiosulphate. Actually, solutions containing 5 c.c. of hydrogen peroxide of known strength, 5 c.c. of 4N-sulphuric acid, and 5 c.c. of 10% potassium bromide solution in 25 c.c. of water were severally treated dropwise with 1, 2, 3, etc., c.c. portions of the sodium nitrite, and the bromine, extracted with 25 c.c. of carbon tetrachloride, was determined. The residual hydrogen peroxide was also determined. The results, Table 5, indicate that the ratios $H_2O_2 : NaNO_2$ in columns 2, 3, and 4 vary with experimentation and always decrease as the nitrite increases.

Table 5, section *A*, shows that the bromine content continues to increase with nitrite addition so long as any peroxide remains. Thereafter, nitrite reacts with the bromine. Column 2 gives the g.-mols. of peroxide used (per g.-mol. of nitrite), and column 3 the g.-mols. of peroxide (per g.-mol. of nitrite) equivalent to the bromine. The difference between the total peroxide used and the amount equivalent to the bromine liberated is given in column 4. If we make the probable assumption that this peroxide is used in oxidising the nitrite to nitrate, and, provided that the peroxide is in excess, the ratio peroxide : nitrite approximates to unity in Table 5 section *A*, but is higher in sections *B* and *C*, suggesting some evolution of oxygen with higher concentrations of peroxide.

TABLE 5.

Column headings: 1, $NaNO_2$ added (c.c.).
2, G.-mols. of H_2O_2 per g.-mol. of $NaNO_2$.
3, Br liberated, calc. as g.-mols. of H_2O_2 per g.-mol. of $NaNO_2$.
4, G.-mols. of H_2O_2 reacting with 1 g.-mol. of $NaNO_2$ (col. 2 − col. 3).

(1)	(2)	(3)	(4)	(1)	(2)	(3)	(4)
	Section A.				*Section* B.		
1·0	2·85	1·83	1·02	1·0	3·27	1·90	1·37
2·0	2·48	1·52	0·96	2·0	2·89	1·78	1·11
3·0	2·48	1·53	0·95	3·0	2·69	1·55	1·14
3·3	2·43	1·43	1·00	4·0	2·61	1·54	1·07
3·6	2·23	1·26	0·97				
4·0	2·01	1·10	0·91		*Section* C.		
5·0	1·61	0·73	0·88	5·0	3·25	1·72	1·53
6·0	1·34	0·40	0·94	10·0	2·95	1·64	1·31
				20·0	2·43	1·21	1·22

In section *A*, 1% $NaNO_2$ solution, 0·472N-H_2O_2; CCl_4 added after the reaction was completed. In section *B*, 1% $NaNO_2$ solution, 0·87N-H_2O_2; CCl_4 present throughout. In section *C*, as in *B* except that 0·1% $NaNO_2$ solution was used.

The formation of pernitrous acid in the reactions of hydrogen peroxide with nitrous acid, nitrogen dioxide, and nitric oxide.

Some observations have been made on the transient yellow coloration in acid solution noted by Trifonow. First, it was found that when dilute peroxide is added to nitrite there is little or no evolution of oxygen; but when the order of addition is reversed oxygen is liberated, the amount increasing with the concentration of the hydrogen peroxide. Secondly, we observed the transient yellow colour by a flow method: hydrogen peroxide–sodium nitrite, flowing through a long glass tube, met at a side arm dilute hydrochloric acid which caused a yellow band to appear in the main stream and extend from just beyond the confluence to a point about 10 cm. further along the tube; the extension varied with the rate of flow. Estimated from the flow rate and the extension of the colour, the life of the pernitrous acid from the mixture used was between 2 and 3 seconds. The yellow liquid, when run into excess of sodium hydroxide, gave a bright yellow colour, stable for many hours. Just beyond the yellow band a vigorous evolution of oxygen took place, but the colourless liquid gave no colour whatsoever when made alkaline. For more detailed examination, the reactants were run down an open "Perspex" trough, instead of a glass tube, so that reagents could be added at any point. Thus it was shown that much bromine was liberated from potassium bromide introduced at any point within the yellow band. When added just beyond the yellow band, however, only a trace of bromine was set free. Hence the oxidation of the bromide ion is probably exclusively due to the pernitrous acid, and not to products resulting from its decomposition.

As might be expected, solutions of the fairly stable, yellow sodium pernitrite result from the rapid addition of acidified peroxide to alkalified nitrite, or when either nitric oxide or nitrogen dioxide is passed into alkaline hydrogen peroxide. The formation of pernitrous acid when nitric oxide reacts with hydrogen peroxide appears not to have been observed before, although it is well known that nitric oxide is oxidised, eventually, to nitric acid, by this treatment. Passing nitric oxide, free from nitrogen dioxide, into alkaline hydrogen peroxide in complete absence of oxygen, gave a yellow colour. The concentration of both sodium hydroxide and hydrogen peroxide was kept low to avoid liberation of oxygen.

We also showed that pernitrous acid is formed, even in acid solution, by bubbling nitric oxide through an acidified solution of hydrogen peroxide and potassium bromide. Much bromine was liberated, which is characteristic of pernitrous acid, whereas no bromine appeared in the absence of hydrogen peroxide and only a trace in the absence of nitric oxide.

Free radicals in reactions involving pernitrous acid.

Reaction between Hydrogen Peroxide and Sodium Nitrite.—The characteristics of the reaction, particularly in the presence of bromide ion, and the evolution of oxygen with certain concentrations of peroxide suggested the possible formation of free radicals. We have demonstrated their occurrence by observing the polymerisation of unstabilised methyl acrylate (Fryling, U.S.P. 2 378 694, states that " peroxynitric acid " initiates the co-polymerisation of diene hydrocarbons and methylene cyanides; this is of interest, but, from the description, his material did not contain pernitrous acid). To a mixture of 10 c.c. of 2% hydrogen peroxide, 1 c.c. of 4N-hydrochloric acid, and 3 c.c. of saturated aqueous methyl acrylate solution in 40 c.c. of water, mechanically stirred and deaërated with a stream of nitrogen, was added drop by drop 5% sodium nitrite solution, also deaërated. The solution became opalescent almost immediately. Polymerisation also occurred with 2 c.c. instead of 3 c.c. of the monomer, but not when the amount of added monomer was reduced to 1 c.c. The associating effect, although evident, was less when the peroxide was added dropwise to acidified nitrite and methyl acrylate. Thus a mixture of 10 c.c. of 5% sodium nitrite solution, 1 c.c. of 4N-hydrochloric acid, and 3 c.c. of saturated aqueous methyl acrylate solution in 40 c.c. of water, stirred and deaërated with nitrogen gave no visible polymerisation when treated, dropwise, with 10 c.c. of 2% deaërated hydrogen peroxide. Nevertheless, with 5 c.c. of monomer present, opalescence appeared towards the end of the addition of the peroxide. But with excess of nitrous acid there was no polymerisation; a deaërated mixture of 10 c.c. of 2% hydrogen peroxide, 10 c.c. of 5% sodium nitrite solution, and 5 c.c. of saturated aqueous monomer solution in 40 c.c. of water was acidified by the rapid addition of dilute hydrochloric acid without evincing evidence of any polymerisation, only the transient yellow colour of the pernitrous acid being observed. Nor did polymerisation take place when very dilute acid was added dropwise to this mixture. Blank experiments omitting each of the three reagents in turn gave no polymerisation.

Reaction between Hydrogen Peroxide and Nitric Oxide or Nitrogen Dioxide.—No polymerisation was met when either nitric oxide or nitrogen dioxide was passed into the acidified monomer solution, but, in the presence of hydrogen peroxide, rapid polymerisation occurred with either oxide of nitrogen, caused, presumably, by pernitrous acid. Polymerisation did not occur when nitric oxide was passed into monomer in alkaline hydrogen peroxide, only the yellow colour of sodium pernitrite being observed.

Acidification of Sodium Pernitrite Solutions.—Various evidence points to the decomposition of pernitrous acid as the source of the free radicals. We have demonstrated their formation by this means by preparing aqueous sodium pernitrite, in the complete absence of hydrogen peroxide, and liberating therefrom pernitrous acid in the presence of methyl acrylate. For this purpose, aqueous sodium azide was ozonised to give sodium pernitrite (method of Gleu and Roell, *loc. cit.*). M-Sodium azide solution was ozonised until azide could no longer be detected with silver nitrate, at which stage, according to Gleu, only sodium pernitrite, nitrite, and nitrate are present. The solution, when deaërated and acidified under air-free conditions, caused the polymerisation of methyl acrylate.

Reaction of the free radicals with benzene.

By using Pernitrous Acid from Hydrogen Peroxide and Nitrous Acid.—The experiments with methyl acrylate showed that excess of nitrous acid must be avoided since it appears to react with either the pernitrous acid or the products of its decomposition. The concentration of hydrogen peroxide must also be kept low as it competes for reaction with the radicals. (N.B. Neither nitrous acid alone nor hydrogen peroxide and unacidified nitrite in the concentrations used affect benzene.) Hence for interaction with benzene a mixture of hydrocarbon (100 c.c.), 5% hydrogen peroxide solution (100 c.c.), 3N-hydrochloric acid (5 c.c.), and water (250 c.c.) was emulsified in a 750-c.c. round-bottomed flask, and 5% sodium nitrite solution (150 c.c.) was added dropwise. All the materials were at room temperature and stirring was continued throughout the addition (about 30 minutes). The molecular ratio hydrogen peroxide : nitrous acid was about 1·5 : 1, thus maintaining the former always in excess. At the end of the run the emulsion was allowed to separate into an aqueous and a benzene layer; both were deep yellowish-brown. Material from twenty such runs on redistilled thiophen-free benzene having been collected, the organic layer was extracted with dilute sodium hydroxide solution until the extract was colourless, washed with water, dried (Na_2SO_4), and distilled under reduced pressure to remove unchanged benzene. The dark brown liquid left (10·5 g.), on fractional distillation, yielded nitrobenzene (10 g.), b. p. 209°, and a small tarry residue.

The residue was sublimed in a vacuum, and the sublimate was separated into two fractions by controlled resublimation. The first fraction, recrystallised from aqueous alcohol, consisted of pure white crystals of diphenyl, m. p. 69°. The mixed m. p. with authentic diphenyl was 69·5°. The second fraction of the sublimate remained yellow when recrystallised from absolute alcohol, had m. p. 172—173°, and proved to be *p*-dinitrobenzene (mixed m. p. 173°).

The alkaline extract of the benzene layer was acidified with concentrated hydrochloric acid and extracted with ether. After drying of the extract and removal of the ether, a dark tarry residue (5·0 g.) remained. Steam-distillation gave crude *o*-nitrophenol (3·25 g.) which, when purified by vacuum-distillation and recrystallisation from aqueous alcohol, had m. p. 45°, not depressed by the authentic compound. The crude *o*-nitrophenol appeared to contain a trace of 2 : 4-dinitrophenol. The tarry residue from the steam-distillation did not sublime in a vacuum but dissolved in hot 6N-sodium hydroxide, from which, on cooling, a small amount of a deep red sodium salt crystallised. Further evaporation and cooling yielded a small amount of a yellow sodium salt. On acidification and extraction with ether the red salt gave a deep yellow phenol, m. p. 68—69°. Reduction with tin and hydrochloric acid produced a very small amount of a light brown, solid amine which became almost white after recrystallisation from chloroform. Its m. p., 200—206°, indicates that it is 3-amino-4-hydroxydiphenyl (m. p. 208°); the nitro-compound was thus 3-nitro-4-hydroxydiphenyl (m. p. 67—68°). The yellow sodium salt on acidification and extraction with ether yielded a very small amount of *p*-nitrophenol which, recrystallised from light petroleum, had m. p. 110—114° slightly raised by admixture with the authentic compound (m. p. 114°).

The original aqueous layer from the reaction was extracted with ethyl acetate. The extract, dried and distilled to remove ethyl acetate, left a tarry residue. Its distillation in a vacuum yielded a small amount of yellow oil, proved qualitatively to be a mixture of *o*-nitrophenol and phenol. Though not readily separated the presence of phenol was demonstrated both by the formation of phenolphthalein with phthalic anhydride, and by the positive reaction to Liebermann's test for phenol.

To sum up, the products were nitrobenzene (10 g.), *o*-nitrophenol (3·25 g.), and, in much smaller quantity, diphenyl, *p*-dinitrobenzene, *p*-nitrophenol, and 3-nitro-4-hydroxydiphenyl. Some evidence has also been obtained for the presence of phenol and 2 : 4-dinitrophenol.

By using Pernitrous Acid from Sodium Azide.—Sodium pernitrite was prepared by ozonising M-sodium azide (200 c.c.), and the orange alkaline solution was emulsified with benzene (100 c.c.) and acidified by adding 3N-hydrochloric acid drop by drop. The benzene and the aqueous layer, both light yellow, were worked up and the former yielded indubitable evidence of nitrobenzene and *o*-nitrophenol. The small yield obtained is believed to be due to the unavoidable presence of so much sodium nitrite which, by producing nitrous acid, tends to destroy much of the pernitrous acid. However, as Gleu and Roell (*loc. cit.*) have shown that a completely ozonised M-azide solution is approximately 0·3N in respect to active oxygen and 0·15M in respect to nitrite, we were able to compare these yields with those derived from peroxide-produced pernitrous acid, in the presence of a similar relative concentration of nitrite. For this purpose, benzene (100 c.c.), hydrogen peroxide (3·4 g.), and sodium nitrite (13·8 g.) in water (200 c.c.) were emulsified. The aqueous portion was thus N with respect to active oxygen and M with respect to nitrite; and, since 1 g.-mol. of hydrogen peroxide reacts with 1 g.-mol. of nitrous acid to form pernitrous acid, these conditions provide the same ratio of pernitrous acid to nitrite as was in the ozonised azide solution, but at concentrations about three times greater. Acidification of the emulsion with 3N-hydrochloric acid produced a yellow colour in both the benzene and the aqueous layer, the colour being only slightly deeper than observed with the ozonised azide. The products of the reaction were isolated and the yields of both nitrobenzene and *o*-nitrophenol proved to be of the same order as those from the ozonised azide.

By using Pernitrous Acid from Nitric Oxide.—A qualitative examination of the materials produced when pure nitric oxide is passed into an emulsion of 5% hydrogen peroxide solution (30 c.c.), water (55 c.c.), 6N-hydrochloric acid (1 c.c.), and benzene (20 c.c.), under air-free conditions, showed the usual products, but, in addition, nitrosophenols were also present.

Discussion

We have shown that the reaction between hydrogen peroxide and nitrous acid is independent of nitrite and directly proportional to nitrous acid and to hydrogen peroxide

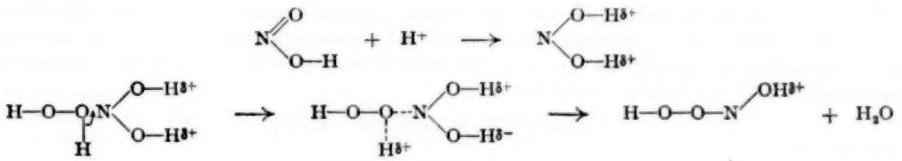
concentrations. The reaction is markedly acid-catalysed. With pernitrous acid as an intermediate the overall reaction has been shown to be

$$HNO_2 + H_2O_2 \longrightarrow HNO_3 + H_2O$$

Evidently from the polymerisation experiments and the array of organic reactions recorded in the following paper free radicals are produced at some stage. We have been at some pains to define as closely as possible where, when, and how these arise. Early suspicions that the free radicals originated in the hydrogen peroxide seemed to be excluded by the fact that the phenomena observed are associated in time and place with the transient brownish-yellow pernitrous acid and are completely ruled out by the fact that they are formed in the absence of hydrogen peroxide. Especially we regard as significant that acidified sodium pernitrite (from azide) produces from benzene an amount of *o*-nitrophenol similar to that produced by an equivalent mixture of nitrite and peroxide. These considerations lead us to favour a scheme in which radicals appear, not in the formation of the pernitrous acid, but in its decomposition :

$$NO_2^- + H^+ \longrightarrow HNO_2 \quad . . . . . \quad (2)$$
$$HNO_2 + H_2O_2 \longrightarrow HO_2NO + H_2O \quad . . . . . \quad (3)$$
$$HO_2NO \longrightarrow HO + NO_2 \quad . . . . . \quad (4)$$
$$HO + NO_2 \longrightarrow HNO_3 \quad . . . . . \quad (5)$$

At low acidities (3) is the rate-determining stage and might be regarded from an esterification angle :



$$HO_2NOH^{\delta+} \longrightarrow HO_2NO + H^+$$

At higher acidities (0·1—0·2N), the rate of formation of pernitrous acid is so fast as to colour the solution and if then the ion NO^+ should appear (which we think extremely unlikely), an alternative mechanism not excluded is :

$$HNO_2 + H^+ \rightleftharpoons H_2O + NO^+$$
$$NO^+ + H_2O_2 \longrightarrow HO_2NO + H^+$$

When hydrogen peroxide is abundant the hydroxyl radicals provide a means of oxygen liberation by such a chain as

$$HO + H_2O_2 \longrightarrow H_2O + HO_2$$
$$H_2O_2 + HO_2 \longrightarrow HO + H_2O + O_2$$

The polymerisation of methyl acrylate may be presumed to follow from the normal functioning of hydroxyl radicals :

$$CH_2{:}CH{\cdot}CO_2Me + {\cdot}OH \longrightarrow HO{\cdot}CH_2{\cdot}\dot{C}H{\cdot}CO_2Me$$
$$HO{\cdot}CH_2{\cdot}\dot{C}H{\cdot}CO_2Me + CH_2{:}CH{\cdot}CO_2Me \longrightarrow HO{\cdot}CH_2{\cdot}CH(CH_2{\cdot}\dot{C}H{\cdot}CO_2Me){\cdot}CO_2Me$$

and the fact that a certain minimum concentration of monomer is necessary finds ready explanation when the chain-breaking properties of the second free radical NO_2 are recalled :

$$HO{\cdot}CH_2{\cdot}\dot{C}H{\cdot}CO_2Me + NO_2 \longrightarrow HO{\cdot}CH_2{\cdot}CH(NO_2){\cdot}CO_2Me$$

We believe the reduction in polymerisation and hydroxylation, found when high concentrations of nitrous acid are present, to be due to the destruction of the per-acid by reduction as it is formed.

When bromide ion is present it is oxidised by the per-acid to bromine. In our view the results in Table 5 confirm the following reaction stages which, while not identical with, are

related to a scheme suggested by Gleu to explain the presence of free bromine in the solution at the end of the reaction :

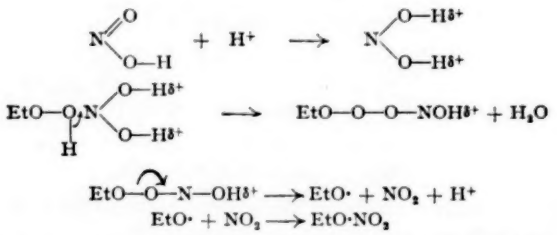
$$H_2O_2 + HNO_2 \longrightarrow HO_2NO + H_2O \quad . . . . . (6)$$
$$HO_2NO + 2HBr \longrightarrow Br_2 + H_2O + HNO_2 \quad . . . . . (7)$$
$$HO_2NO \longrightarrow HNO_3 \quad . . . . . (8)$$
$$HNO_2 + Br_2 + H_2O \longrightarrow HNO_3 + 2HBr \quad . . . . . (9)$$

The figures in columns 3 and 4 of Table 5 are then a measure of stages (7) and (8) respectively; their ratio gives a rough idea of the relative rate of these two reactions at the concentrations used. The decrease in peroxide reacting and in bromine liberated (per g.-mol. of nitrite) observed as the amount of nitrite is increased is evidently caused by the prominence of process (9) at higher concentrations of free bromine. Some bromine may arise by the intervention of the hydroxyl radical (that the electron transfer $OH + Br^- \longrightarrow Br + OH^-$ is possible was demonstrated by the strong discharge of bromide ion which took place when we added dilute ferrous sulphate to an acidified peroxide–bromide mixture), but tests made during the flow experiment led us to believe that most of the oxidation should be ascribed to the per-acid itself. The maximum liberation of bromine occurs just at the point where all the hydrogen peroxide has been used up. The actual ratio of hydrogen peroxide to nitrous acid used at this point depends on the relation of the several competing reactions and is not, as Trifonow (*loc. cit.*) assumed, the stoicheiometric one for the formation of pernitrous acid.

The formation of alkyl nitrates by the reaction between ethyl hydroperoxide and alkyl nitrites has been explained by Baeyer and Villiger (*loc. cit.*) as due to the formation of an intermediate addition compound. The postulated mechanism for the reaction between hydrogen peroxide and nitrous acid appears to indicate, however, that the main processes occurring in Baeyer's reaction may be :

$$EtO{\cdot}NO + H_2O \longrightarrow EtOH + HNO_2$$

followed by



These stages are not incompatible with the products isolated by Baeyer and Villiger and it is notable that when these workers substituted hydrogen peroxide for the ethyl hydroperoxide the products contained no alkyl nitrate but some aldehyde. In this case we should expect pernitrous acid which would be capable of oxidising the alcohol to aldehyde.

Not much may be usefully said of the recent paper by Abel (*loc. cit.*) since it is based on the assumption that the yellow compound herein described is a solution of nitrogen dioxide in water. Actually nitrogen dioxide dissolves in water to give a colourless solution and, indeed, only shows its colour when in the form of gas either in the bubbles within the saturated aqueous solution or above it. Of the difference between an aqueous solution of nitrogen dioxide and pernitrous acid the present writers have no doubt.

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169. *The Nitration and Hydroxylation of Aromatic Compounds by Pernitrous Acid.*

By E. Halfpenny and P. L. Robinson.

The reaction between pernitrous acid and a number of simple aromatic compounds is described. Both hydroxylation and nitration occur and diphenyl derivatives have been isolated. The products are mainly *m*-nitro-compounds, *o*- and *p*-hydroxy-compounds, or derivatives of *o*-nitrophenol.

Hydroxylation is considered to be due to hydroxyl radicals produced by the homolytic fission of pernitrous acid, and nitration to be due to nitrogen dioxide reacting with the free aryl radicals present in the solution.

Trifonow (*Z. anorg. Chem.*, 1922, **124**, 123, 136) observed that when benzene is shaken with nitrous acid and hydrogen peroxide both the organic and the aqueous layer become yellow. Alkali changed the colour to red, from which he assumed the formation of *o*-nitrophenol, and he suggested this reaction for detection of benzene in other hydrocarbons. Ficklen and Cook (*ibid.*, 1933, **211**, 141) determined the sensitivity of this test.

We have reported (preceding paper) that the decomposition of pernitrous acid releases free hydroxyl radicals, the evidence being the polymerisation of methyl acrylate and the hydroxylation of benzene. We believe that the radicals arise from the homolytic fission of the unstable pernitrous acid. In addition to phenolic compounds, benzene yielded appreciable quantities of nitrobenzene. Nitration in aqueous media of very low acidity (approximately N/30) at room temperature seemed sufficiently remarkable to call for further investigation. The reaction proves to be of considerable generality. Nearly always the nitro-group enters the ring at the *meta*-position relative to an existing substituent. When both hydroxyl and nitro-group enter the ring together, the hydroxyl appears, almost without exception, *ortho* and *para* in respect to an original substituent, with the nitro group adjacent to the hydroxyl. A compound of particular interest found among the products is diphenyl: although it occurs in small quantity, its formation evidently has an important bearing on any explanation which may be advanced to account for these hydroxylations and nitrations.

We show that acidity decreases during the reaction and that the decrease is quantitatively related to the extent of nitration.

We believe the first stage in this nitration process to be an attack by the hydroxyl radical on the aromatic compound with the formation of a free aryl radical; and the second to be a combination of this aryl radical with nitrogen dioxide, the other radical produced by the rupture of the pernitrous acid. Unsuccessful attempts have been made to identify the aryl radicals by having either iodine or nitric oxide present in the reaction system.

The yield of nitrated and hydroxylated compounds, based on the nitrite used, is less than 10%, except for anisole. With some compounds appreciable tar appears in the product. Various changes in conditions, made to increase the yield, were unsuccessful.

Experimental

The Reaction with Toluene, Nitrobenzene, Dimethylaniline, Phenol, Anisole, and Chlorobenzene.—Aromatic compounds were brought into contact with decomposing pernitrous acid by vigorously agitating them with a slightly acid solution of hydrogen peroxide and adding sodium nitrite solution. To compare products and yields with those from benzene already reported, the same quantities, concentrations, and methods of mixing were used throughout. The aromatic compound (100 c.c.) was emulsified with 5% hydrogen peroxide solution (100 c.c.), 3N-hydrochloric acid (5 c.c.), and water (250 c.c.) in a 750-c.c. round-bottomed flask. 5% Sodium nitrite solution (150 c.c.) was added dropwise to the rapidly stirred mixture. With phenol, the quantity of nitrite was reduced to avoid the evolution of oxides of nitrogen. Only the organic phase was examined and, since the yields are small, many runs were necessary to get sufficient material for examination. The products from the various experiments are listed in Tables 1 and 2 (p. 942).

Toluene. A light yellowish-brown colour developed in both the aqueous and the organic

layer. The organic material from fifty runs, on redistilled toluene, was extracted with dilute sodium hydroxide solution and, after being washed with water, further extracted with saturated sodium hydrogen sulphite solution. After being further washed with water and dried (Na_2SO_4), the toluene was removed by vacuum-distillation, to leave a dark liquid (9·5 g., equiv. to 0·2 g. per run). Distilled at 5 mm. this gave a yellow liquid and a tarry residue (1 g.). The distillate, from infra-red analysis, appeared to consist of nitrotoluene 20, halogeno-compounds (probably benzyl chloride) 30, benzaldehyde 7, and nitrocresol 9%. (The last two are present owing to incomplete extractions by sodium hydroxide and sodium hydrogen sulphite.)

The bisulphite solution was treated with excess of sodium carbonate and extracted with ether. The dried ethereal extract, on evaporation, left a residue (2·0 g., equiv. to 0·04 g. per run). The residue gave a colourless distillate (1·5 g.; b. p. 179°), identified as benzaldehyde by the preparation of its phenylhydrazone (m. p. 156—158°; lit., 158°) and 2 : 4 dinitrophenylhydrazone (m. p. 236°; lit., 235°) and of benzoic acid (m. p. 121°; lit., 121°).

The alkaline extract, washed with ether to remove traces of toluene, was acidified and extracted with ether. The extract after drying and removal of the ether, left a residue of phenolic compounds (12·5 g., equiv. to 0·25 g. per run); this on steam-distillation gave a semi-solid, separable by filtration into a yellow crystalline solid (3 g.) and a light brown oil (7·5 g.). The first, recrystallised from aqueous alcohol, had m. p. 69°, and was identified as 2-methyl-6-nitrophenol by mixed m. p. and by its acetate (m. p. 41·5°; lit., 42°). The oil (m. p. *ca.* 10°) was a mixture. Attempts at separation failed, but the benzoate (Schotten–Baumann) crystallised from alcohol as fine needles, m. p. 98—99°, and served to identify the chief constituent of the oil as 4-methyl-2-nitrophenol (benzoate, m. p. 100—101°). The tarry residue from the steam-distillation, when distilled in a vacuum, gave a small amount of white material. This crystallised from water in an unstable form which melted at a low temperature and then resolidified, suggesting that it was 2-methyl-4-nitrophenol, a deduction rendered probable by the stable phase melting at 95° (lit., 96°).

Nitrobenzene. The deep yellowish-orange organic material from twenty runs on AnalaR nitrobenzene was extracted with sodium hydroxide solution, washed, dried, and distilled in a vacuum. The residue (15·8 g., equiv. to 0·8 g. per run), on steam-distillation, gave 14·6 g. of crude *m*-dinitrobenzene. Infra-red analysis showed that it contained *m*- 91, *p*- 5, and *o*-dinitrobenzene 4%. The black, tarry residue from the steam-distillation, when heated in a vacuum, gave a small crystalline sublimate (m. p. 198—199° when recrystallised from alcohol) which was probably 3 : 3′-dinitrodiphenyl.

The phenolic substances (14·5 g., equiv. to 0·7 g. per run) from the alkaline extract gave, on steam-distillation, *o*-nitrophenol (2·0 g.; m. p. 45° after recrystallisation from aqueous alcohol; m. p. not depressed by authentic *o*-nitrophenol). The residual solution from the steam-distillation, treated with concentrated sodium hydroxide solution, precipitated the sodium salts of *m*- and *p*-nitrophenol which were fractionally crystallised from 10% sodium hydroxide solution to yield crude *p*- (2·8 g.) and *m*-nitrophenol (0·66 g.). By recrystallisation from dilute hydrochloric acid (charcoal), the *m*-nitrophenol had m. p. 96—97° (lit., 96°) and the *p*-nitrophenol, m. p. 112—114° (lit., 114°). The respective benzoates had m. p.s 93—95° and 142°. This (somewhat crude) separation indicated that the three isomeric nitrophenols are present in the approximate proportions *p*- 51, *o*- 37, and *m*-nitrophenol 12%.

On acidification of the strongly alkaline filtrate from the sodium salts of *m*- and *p*-nitrophenol, a black precipitate formed which was separated and dissolved in alcohol. The mother-liquor was extracted with ether, and the ethereal extract was added to the alcoholic solution. Removal of the solvents left a black, tarry residue which, when heated, yielded a very small sublimate (m. p. 171—172°), possibly 4-hydroxy-3 : 4′-dinitrodiphenyl.

Dimethylaniline. Nine runs were made on AnalaR dimethylaniline (commercial dimethylaniline gave a purple colour due to crystal-violet), and the organic material, after extraction with sodium hydroxide, was dried and distilled, leaving a residue (12 g., equiv. to 1·3 g. per run). This was distilled at 22 mm. and gave, at 125°, a distillate (4·5 g.) which was steam-distilled to remove any dimethyl-*p*-nitroaniline, and then extracted with ether from a slightly acid aqueous solution to remove most of the remaining dimethylaniline. The yellow oil thus obtained was crude dimethyl-*o*-nitroaniline (hydrochloride, decomp. 172—173°; lit., 173—174°). Reduction of the nitro-compound yielded a diamine giving the characteristic colour reactions of *o*-aminodimethylaniline.

The residue remaining after distillation of the dimethyl-*o*-nitroaniline was extracted with alcohol, and the extract freed from tar by boiling it with animal charcoal. Removal of the alcohol left a mixture which was separated by fractional precipitation from an acid solution by

means of alkali. The two fractions, subsequently recrystallised from alcohol, gave dimethyl-*p*-nitroaniline (0·32 g.; m. p. 163·5°) and fairly pure tetramethylbenzidine (0·46 g.; m. p. 189—191°) respectively. Both compounds were further characterised by colour reactions.

The phenolic material (0·87 g., equiv. to 0·1 g. per run) from the alkaline extract, when extracted with ether, left a yellow, unidentified, insoluble solid (0·16 g.) which, after recrystallisation from acetone, melted at 210° with vigorous decomposition.

Phenol. Ten runs were made, each with 10 g. of phenol. The acidified phenol–hydrogen peroxide mixture was at 40°, whereby the former was kept almost completely in solution. Only 50 c.c. of 5% sodium nitrite solution were used in each run because more caused vigorous evolution of nitrous fumes. The brown aqueous solution from ten runs was extracted with ether, and the ethereal solution was dried. This ethereal solution, distilled to remove the ether and unchanged phenol, left a semi-solid, tarry residue (25·5 g., equiv. to 2·5 g. per run). The residue, dissolved in hot 6N-sodium hydroxide, yielded on cooling a small amount of a crystalline yellow sodium salt which, reconverted into the phenol and recrystallised, proved to be *p*-nitrophenol (m. p. 110°) (benzoate, m. p. 142°).

The alkaline filtrate from the sodium salt of *p*-nitrophenol was acidified and extracted with ether. The dried ethereal solution on evaporation left a residue which was fractionally distilled in a vacuum. The first fraction, a low-melting, yellow solid (possibly *o*-nitrophenol and phenol), was reduced with alkaline sodium dithionite (hydrosulphite) and gave a benzoate which, after recrystallisation melted partly at 65° and completely at 155°, suggestive of a mixture of the benzoates of phenol (m. p. 68°) and *o*-aminophenol (m. p. 182°). The second fraction, a light yellow solid (2·5 g.) becoming almost white (m. p. 102—104°) after recrystallisation from dilute hydrochloric acid, was identified as catechol by preparation of the dibenzoate (m. p. 85—86°; lit., 86°), a mixed m. p. with authentic catechol (101—104°), the green colour with ferric chloride, and an immediate white precipitate with lead acetate. The third fraction, a very pale yellow solid (2·0 g.) becoming white (m. p. 170—171°) when recrystallised, was identified as quinol by preparation of the diacetate (m. p. 122—123°; lit., 123°).

Anisole. The yellow-orange organic material from twenty runs was extracted with sodium hydroxide solution, dried, and distilled, leaving a trace of tar from which nothing significant was isolated.

The sodium hydroxide solution, after acidification, was extracted with ether which when dried and evaporated left a residue (60 g., equiv. to 3 g. per run). This, distilled in a vacuum, gave three fractions (*a*), (*b*), and (*c*). The first, (*a*), a light yellow solid (30 g.), gave on recrystallisation colourless needles (m. p. 41°) from which a benzoate (m. p. 68°) was prepared, proving that it was phenol with, perhaps, traces of *o*-nitrophenol. Fraction (*b*), a low-melting yellow solid (8·0 g.), was, from qualitative tests, evidently mainly *o*-nitrophenol, a view confirmed by the dibenzoate derivative (m. p. 181—182°; lit., 182°), made by reduction with alkaline sodium dithionite to *o*-aminophenol and treatment thereof with benzoyl chloride. Fraction (*c*), an orange semi-solid material (7·7 g.), gave, when recrystallised, 4-methoxy-2-nitrophenol (5 g.; m. p. 80°), identified by its benzoate (m. p. 89—90°; lit., 89°). The mother-liquor yielded a small amount of another crystalline substance (m. p. 55—60°) probably impure 6-methoxy-2-nitrophenol.

Chlorobenzene (Experimental work by J. J. Hillary). Redistilled chlorobenzene (100 c.c.), 2·5% hydrogen peroxide solution (380 c.c.), and 2·5N-hydrochloric acid (5 c.c.) were mechanically mixed, and 5% sodium nitrite solution (150 c.c.) was added dropwise. The bright yellow, organic material from seventy-two such runs, after extraction with sodium hydroxide solution, drying, and removal of the chlorobenzene, left a residue (29·5 g., equiv. to 0·4 g. per run). This residue, when distilled in a vacuum, gave a distillate (24 g.) which solidified on cooling and was proved to be crude *m*-chloronitrobenzene (m. p. 44—45° after recrystallisation) by reduction to *m*-chloroaniline and preparation of the benzoyl derivative (m. p. 122°). By fractionally crystallising the crude *m*-chloronitrobenzene from aqueous alcohol, a small amount of *p*-chloronitrobenzene (m. p. 83°) was separated and identified by reduction to *p*-chloroaniline (m. p. 68°).

The phenolic material from the alkaline extract (21 g., equiv. to 0·3 g. per run) gave, when distilled, a quantity of light yellow, volatile liquid distillate with the properties of crude *o*-chlorophenol. The residue, recrystallised from benzene, gave a bright yellow crystalline substance (m. p. 86—87°) identified as 4-chloro-2-nitrophenol by the acetate (m. p. 48°).

Change in Acidity during the Reaction and its Quantitative Relation to the Product.—Our view of the nitration brought about by this reaction (see p. 943) implies a fall in acidity during its course. This assumption has been confirmed experimentally for nitrobenzene, chlorobenzene, and benzene.

TABLE 1. *Non-phenolic products.*

Starting material	Major products	Minor products
C_6H_6	$PhNO_2$	Ph_2, p-$C_6H_4(NO_2)_2$
PhMe	$C_6H_4Me{\cdot}NO_2$, PhCHO, halogeno-compounds	—
$PhNO_2$	m-$C_6H_4(NO_2)_2$	o- and p-$C_6H_4(NO_2)_2$, (3-$NO_2{\cdot}C_6H_4{\cdot})_2$
$PhNMe_2$	o- and p-$NO_2{\cdot}C_6H_4{\cdot}NMe_2$	—
	(p-$Me_2N{\cdot}C_6H_4)_2$	
PhCl	m-$C_6H_4Cl{\cdot}NO_2$	p-$C_6H_4Cl{\cdot}NO_2$

TABLE 2. *Phenolic products.*

Starting material	Major products	Minor products
C_6H_6	o-$NO_2{\cdot}C_6H_4{\cdot}OH$	3 : 1 : 4-$NO_2{\cdot}C_6H_3Ph{\cdot}OH$
		PhOH, p-$NO_2{\cdot}C_6H_4{\cdot}OH$
		[2 : 4 : 1-$(NO_2)_2C_6H_3{\cdot}OH$]
PhMe	6 : 2 : 1- and 2 : 4 : 1-$NO_2{\cdot}C_6H_3Me{\cdot}OH$	4 : 2 : 1-$NO_2{\cdot}C_6H_3Me{\cdot}OH$
$PhNO_2$	o-, m-, and p-$NO_2{\cdot}C_6H_4{\cdot}OH$	3 : 4-$NO_2{\cdot}C_6H_3(OH){\cdot}C_6H_4{\cdot}NO_2$-$p$
$PhNMe_2$	—	Unidentified substance (m. p. 210°, decomp.)
PhCl	o-$C_6H_4Cl{\cdot}OH$	—
	2 : 4 : 1-$NO_2{\cdot}C_6H_3Cl{\cdot}OH$	
PhOH	o- and p-$C_6H_4(OH)_2$	o- and p-$NO_2{\cdot}C_6H_4{\cdot}OH$
PhOMe	PhOH, o-$NO_2{\cdot}C_6H_4{\cdot}OH$,	2 : 6 : 1-$NO_2{\cdot}C_6H_3(OMe){\cdot}OH$
	2 : 4 : 1-$NO_2{\cdot}C_6H_3(OMe){\cdot}OH$	

Nitrobenzene. 5% Sodium nitrite solution (150 c.c.) was added dropwise to an emulsion of 6% hydrogen peroxide solution (100 c.c.), water (250 c.c.), 2·46N-hydrochloric acid (5 c.c.), and nitrobenzene (100 c.c.). Afterwards the pH of the aqueous layer was measured at a glass electrode. In three experiments, the hydrogen-ion concentration changed from 0·012 g.-ion per 500 c.c. at the beginning to 0·007 g.-ion at the end, *i.e.*, 0·005 g.-ion of hydrogen had been used per run.

If it is assumed that the fall in acidity is related to nitration as $HCl \equiv HO_2{\cdot}NO \equiv C_6H_4(NO_2)_2$ and that the relation is reasonably quantitative, then the weight of *m*-dinitrobenzene to be expected would be 0·84 g. per run, which is remarkably close to the 0·80 g. actually isolated.

Chlorobenzene. By similar measurement and calculation for chlorobenzene, the significant product from which is *m*-chloronitrobenzene (the *o*-chlorophenol does not affect the issue), the hydrogen ion used proved to be equivalent to 0·35 g. of this compound. The actual yield of *m*-chloronitrobenzene was 0·4 g.

Benzene. The formation of both nitrobenzene and *o*-nitrophenol would be expected to contribute to the reduction in acidity. It being borne in mind that they are found in the proportion 2 : 1, the calculated weight of nitrated material should have equalled 1·0 g. which, again, is not remote from the 0·76 g. found under corresponding conditions.

Factors Influencing Yields.—In view of preparative possibilities the relation between yield and conditions was examined for nitrobenzene.

Hydrogen-ion concentration. Increasing the acidity reduces yields of both phenolic and non-phenolic products:

	Non-phenols (g.)		Phenols (g.)	
Initial $[H^+]$ (g.-ion/l.)	Run 1	Run 2	Run 1	Run 2
0·291	0·35	0·32	0·50	0·28
0·063	0·91	0·86	0·66	0·63

Hydrogen peroxide. The reaction is not very sensitive to this reagent, but a twelve-fold increase in concentration showed evident reduction in yield:

Initial $[H_2O_2]$ (g./l.)	20·2	253·0
Non-phenols (g.)	0·91	0·42
Phenols (g.)	0·68	0·50

Sodium nitrite. (*a*) Rate of addition. Three runs, with nitrite of different concentrations but with the same amount of reagent in every case, showed that the changes were without appreciable influence:

$[NaNO_2]$ (g./l.)	300	150	50
Non-phenols (g.)	0·92	0·92	0·91
Phenols (g.)	0·63	0·58	0·66

(*b*) Total amount used. The yields of both hydroxylated and nitrated compounds appear to be proportional to nitrite added, provided that hydrogen peroxide is in excess throughout:

5% $NaNO_2$ added (c.c.)	150	100	50
Non-phenols (g.)	0·82	0·66	0·21
Phenols (g.)	0·70	0·57	0·16

Temperature. The yield of hydroxylated and nitrated material increases with temperature, but a greater amount of tar is formed :

	Non-phenols (g.)		Phenols (g.)	
Temp.	Run 1	Run 2	Run 1	Run 2
8—13°	0·94	0·86	0·59	0·71
50—55°	1·60	1·50	0·91	0·95
98°	1·77	1·81	1·17	1·25

Hydrogen, nitrogen, air. When blown through the reactants hydrogen appeared to reduce the yield of hydroxylated material; neither nitrogen nor air had significant effect :

	Non-phenols (g.)		Phenols (g.)	
Conditions	Run 1	Run 2	Run 1	Run 2
Rapid air stream	0·99	0·88	0·69	0·61
Rapid H_2 stream	1·05	1·03	0·41	0·48
Rapid N_2 stream	1·17	1·16	0·56	0·56
Normal	1·04	1·13	0·67	0·69
	1·07 *		0·63 *	

* Run 3.

Order of addition of reagents. Yields did not differ appreciably when (*a*) a mixture of hydrogen peroxide and sodium nitrite was added to acidified nitrobenzene or (*b*) sodium nitrite was added to a mixture of nitrobenzene and acidified hydrogen peroxide. They did differ considerably, however, when (*c*) hydrogen peroxide was added to acidified nitrite and nitrobenzene (table below). With nitrite in excess throughout, the products were all greatly reduced in amount and associated with more tar.

	Non-phenols (g.)		Phenols (g.)	
Method of mixing	Run 1	Run 2	Run 1	Run 2
(*a*)	0·76	0·83	0·76	0·76
(*b*)	0·87	0·71	0·80	0·78
(*c*)	0·27	0·16	0·31	0·21

Emulsifiers. The various types used (fatty alcohol–polyethylene oxide condensates and polyglyceryl ricinoleate), although they increased the dispersion, did not increase the yield of either hydroxylated or nitrated material.

Discussion

We showed (preceding paper) that a typical aromatic compound, benzene, is nitrated and hydroxylated by dilute solutions of pernitrous acid, whether prepared by using hydrogen peroxide or not, and further that these reactions take place at low acidity and laboratory temperatures. We concluded that the reactions resulted from the presence of two free radicals—hydroxyl and nitrogen dioxide—and experimental work described above has tended throughout to confirm these inferences. At an early stage we were led to dismiss any idea of the nitronium ion NO_2^+ on account, first, of its being a highly improbable species in acidities of the order of N/30, and, secondly, because the products of certain nitrations, for example, *m*-chloronitrobenzene from chlorobenzene, are not those formed in nitrations which may, with certainty, be ascribed to the action of the nitronium ion. We have satisfactory evidence that the nitration does not proceed through the formation of a nitroso-compound, by the action of the nitrosyl ion NO^+, and its subsequent oxidation to a nitro-compound.

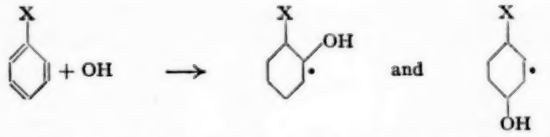
In the nitrous acid–hydrogen peroxide reaction with aromatic compounds the hydroxylation is nearly always *ortho* and *para* to the original substituent which appears to be in accord with recent views on radical substitution in aromatic compounds (Augood, Hey, Nechvatal, and Williams, *Nature*, 1951, **167**, 725). Exceptions are *m*-nitrophenol from nitrobenzene (but the amounts found are much smaller than those for either *o*- or *p*-nitrophenol) and some of the other minor products from this and other starting materials. Nitration, on the other hand, except for dimethylaniline, is almost exclusively *meta* to the original substituent. When, however, there is simultaneous hydroxylation and

nitration the incoming groups occupy adjacent positions in all the major products. Attempts to account for the above facts have led us to choose radical addition rather than hydrogen replacement as a basis of the general scheme, albeit speculative, advanced below. This or any other interpretation must start from the point that our reaction products cannot be due to ionic-substitution processes.

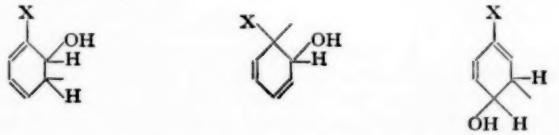
(*a*) The pernitrous acid undergoes homolytic fission :

$$HO_2{\cdot}NO \longrightarrow HO + NO_2$$

(*b*) The hydroxyl radical enters the aromatic nucleus (almost exclusively) in the *ortho* and the *para*-position :

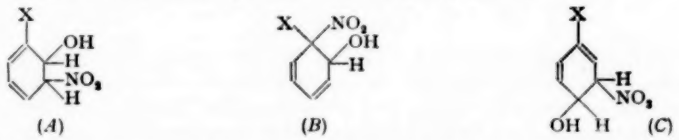


In the radicals formed, the unpaired electron will probably be localised in the position adjacent to the hydroxyl group :

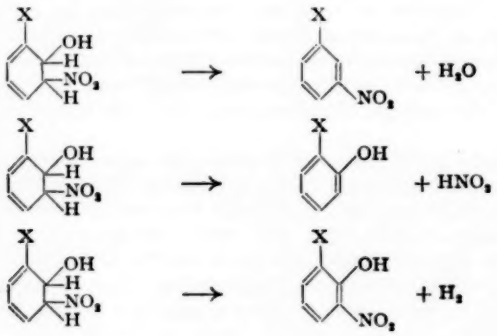


but the possibility of the formation of quinonoid structures is not excluded :

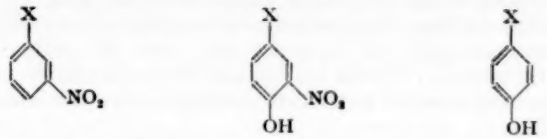
(*c*) By reaction between these free aryl radicals and nitrogen dioxide, for which the activation energy will be practically zero, the nitro-group is attached :



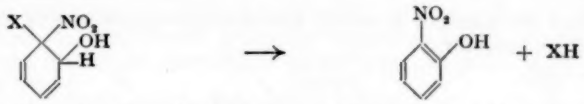
(*d*) These addition compounds are unstable and liable to break down by the elimination of water, of nitrous acid, or of hydrogen, *e.g.*, in (*A*) :



Similarly (*C*) will give



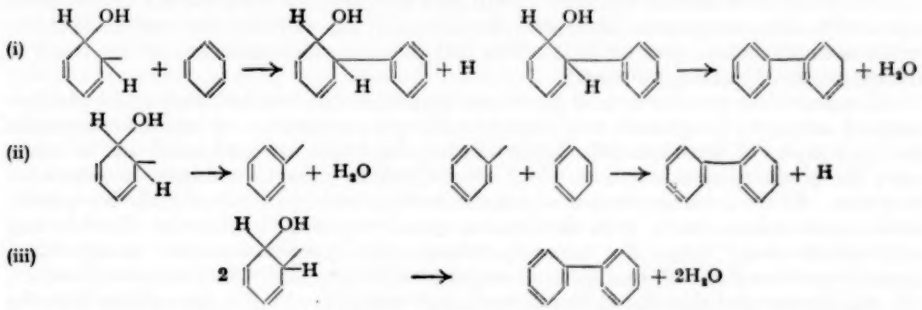
But in the case of (*B*) the same type of reaction renders possible the elimination of the original substituent X :



The purely hydroxylated products may result from a more direct process, *e.g.* :

By such means hydroxyl and nitro-groups may be introduced, individually or together, into the aromatic molecule. The hydroxyl group will always enter in the *ortho-* or *para*-position, and the nitro-group in the *meta*-position, relative to the original substituent. When both hydroxylation and nitration occur, hydroxyl and nitro-groups will be adjacent to one another, unless the intermediate aryl radical should adopt the quinonoid structure, when the nitro-group will take up a position *para* to the hydroxyl. The course of the decomposition of the addition compound depends somewhat on the nature of the original substituent which thus determines the product.

With benzene these suggestions account satisfactorily for the major products nitrobenzene and *o*-nitrophenol, and also for the two minor products, phenol and *p*-nitrophenol. The diphenyl isolated may result from one or more of the following sequences (owing to the presence of nitrogen dioxide concurrently with the aryl radical it is not to be expected that diphenyl will occur in more than a small quantity) :



Speculation as to the way in which the minor products *p*-dinitrobenzene and 4-hydroxy-3-nitrodiphenyl are formed is perhaps not profitable at this stage.

Of the toluene products the nitrotoluene, 2-methyl-6-nitrophenol and 4-methyl-2-nitrophenol may well result from the operation of such a scheme as that outlined above. The benzaldehyde probably springs from the direct oxidation of toluene by the pernitrous acid. Formation of the halogeno-compound suggests the presence of chlorine atoms, presumably from the discharge of chloride ions.

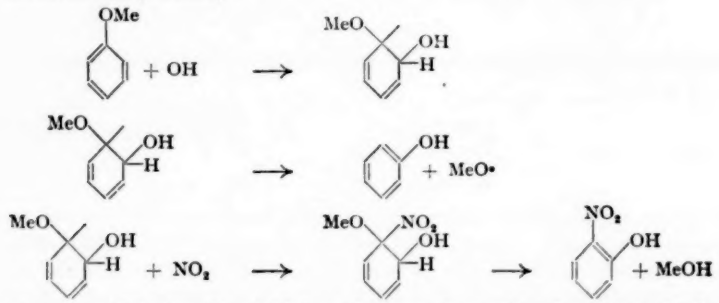
The formation of some *m*-nitrophenol from nitrobenzene indicates that here, at least, the hydroxyl radical does not enter the aromatic nucleus exclusively in the *ortho-* and

para-positions. The probable mode of formation of the other major products from nitrobenzene comes readily within the general scheme outlined above.

The compounds derived from dimethylaniline are anomalous, but may be explained in view of the fact that Bamburger and Tschirner (*Ber.*, 1899, **32**, 1897) obtained the same product simply by the action of nitrous acid on dimethylaniline oxide. It is conceivable that the hydrogen peroxide oxidised the dimethylaniline to the oxide which in turn reacted with the nitrous acid.

The major products obtained from chlorobenzene and phenol present no anomalies. Phenol is interesting in that the dominant compounds are catechol and quinol, not nitrophenols.

Anisole provides an example in which the original substituent is eliminated. The reactions involved are probably :



In the presence of iodine the yield from benzene is much reduced but the hope that it would successfully compete with nitrogen dioxide for aryl radicals, and thus serve to identify them, was not realised. One halogeno-compound, 6-iodo-2-nitrophenol, was isolated but the manner of its formation is unknown.

Nitric oxide, also sent on the same quest, when present during the reaction with benzene, led to the formation of some nitrosophenol. This may be caused by the gas combining with either the phenolic products or the aryl radicals. A possibility, regarded as unlikely, is the concurrent formation of the nitrosyl ion and hydroxyl radical, $NO + H_2O_2 \longrightarrow NO^+ + OH + OH^-$, followed by nitrosation of the aromatic compounds.

The presence of nitroso-compounds here, and the fact that they are not immediately oxidised to nitro-compounds, taken with the absence of any evidence of nitroso-compounds in the normal reaction, goes far to establish that the nitro-compounds are not the result of the oxidation of nitroso-compounds.

It appears that pernitrous acid provides a general method for nitration and hydroxylation of aromatic compounds and especially for the preparation of *m*-nitro-compounds and derivatives of *o*-nitrophenol. Unfortunately the yields are very small and in many cases the products include species which are difficult to separate and may be associated with tars. Of the aromatic compounds used, nitrobenzene and anisole gave the best yields, based on the nitrite used ; with nitrobenzene about 8% of the nitrite was effective, and with anisole about 30%. For benzene, toluene, and chlorobenzene the corresponding figure is less than 6%. Phenol gives a comparatively high yield of hydroxylated product, but this is most probably due to its relatively high solubility. It has been shown that the yield in the case of nitrobenzene (the only compound fully investigated) cannot be improved by altering the concentration or the method of mixing. Raising the temperature increased the yield, but the product contained considerably more tar.

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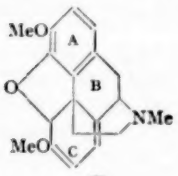
KING'S COLLEGE, NEWCASTLE-ON-TYNE. [*Received, September 4th*, 1951.]

170. *The Structure of Phenyldihydrothebaine.*

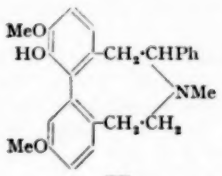
By K. W. Bentley and Sir Robert Robinson.

The structure (II) of phenyldihydrothebaine, deduced from existing data on theoretical grounds, has been confirmed by oxidation of the base to benzaldehyde, benzoic acid, and 4-methoxyphthalic acid, and by exhaustive methylation of its methyl ether to a nitrogen-free substance that yields 5 : 6 : 5′-trimethoxydiphenic acid and the corresponding dialdehyde on oxidation with permanganate, and the same aldehyde on ozonolysis. Thebaine has been shown to react with anhydrous magnesium iodide, the product on reduction with lithium aluminium hydride being converted into a sensitive phenolic base.

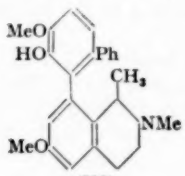
The reaction between thebaine and phenylmagnesium bromide was first investigated by Freund (*Ber.*, 1905, **38**, 3234; D.R.-P., 181 510/1907; Frdl., **8**, 1171) who obtained in this way a phenolic base $C_{25}H_{27}O_3N$ which he called phenyldihydrothebaine. Subsequent investigations (Freund, *loc. cit.*; Freund and Holtoff, *Ber.*, 1916, **49**, 1287; Small, Sargent, and Bralley, *J. Org. Chem.*, 1947, **12**, 847) on this and on the corresponding methyldihydrothebaine (Small and Fry, *J. Org. Chem.*, 1939, **3**, 509) revealed that these compounds show remarkable chemical properties, inexplicable on the basis of any structure derived from the Gulland–Robinson formula for thebaine (I) unless a deep-seated rearrangement is assumed



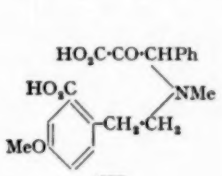
(I)



(II)



(III)

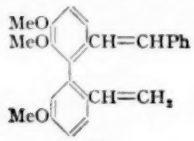


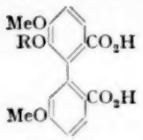
(IV)

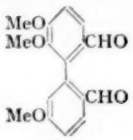
to occur during the entry of the phenyl group, an explanation rejected by Small, Sargent, and Bralley (*loc. cit.*) and by Small and Fry (*loc. cit.*).

A structure that appeared to embrace all the known facts was advanced by Robinson (*Proc. Roy. Soc.*, 1947, *B*, **135**, 14; *Nature*, 1947, **160**, 815), the evidence for which may be summarised as follows. The peculiar properties of phenyldihydrothebaine (resistance to hydrogenation; stability towards acids; retention of the vinyl group during exhaustive methylation) clearly indicate that in this substance the near-aromatic ring of thebaine has become fully aromatic. On this assumption it can be shown that the nitrogen-free product obtained by exhaustive methylation of phenyldihydrothebaine cannot owe its optical activity to the presence of an asymmetric carbon atom, and must therefore owe it to some other cause of molecular dissymmetry, most plausibly to restricted rotation about a carbon–carbon bond, probably in a diphenyl system. On the basis of these arguments, and a reasonably probable course for the Grignard reaction, the structure (II) was suggested for phenyldihydrothebaine. The objection of Small, Sargent, and Bralley (*loc. cit.*), that the ultra-violet absorption spectra of phenyl- and methyl-dihydrothebaine do not indicate the presence of a second aromatic ring in conjugation with the first in these compounds, is invalidated by the work of Picket, Walter, and France (*J. Amer. Chem. Soc.*, 1936, **58**, 2296) and O'Shaugnessy and Rodebush (*ibid.*, 1940, **62**, 2906) who showed that non-coplanar diphenyls do not exhibit typical diphenyl absorption in the ultra-violet, but only absorption characteristic of isolated aromatic nuclei. The structure (III) for phenyldihydrothebaine, considered for a short time, was rejected as it contains an unrestricted diphenyl system. The stages in the development of the argument are given in more extended form in an Anniversary Address to the Royal Society (*loc. cit.*) and an excellent account is included in Fieser and Fieser's "Natural Products Related to Phenanthrene," A.C.S. Monograph No. 70, pp. 19—22.

Confirmation of the structure (II) for phenyldihydrothebaine has been sought and obtained by permanganate oxidation of the base, which affords benzaldehyde (showing that the phenyl group is present as PhCH–), benzoic acid, and 4-methoxyphthalic acid (showing that ring C of thebaine has become aromatic in phenyldihydrothebaine, and bears no additional substituent), the latter being identified with an authentic specimen by mixed melting points of the acid, anhydride, and *N*-methylimide. In addition an amino-acid, inadequately characterised, was obtained; analytical data for the copper derivative of this acid agree closely with the values required for the copper salt of (IV). Exhaustive methylation of phenyldihydrothebaine methyl ether yielded an optically active substance (+)-3 : 4-dimethoxy-2-(5-methoxy-2-vinylphenyl)stilbene (V) (prepared by Freund,


(V)


(VI)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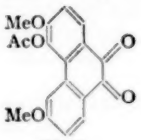
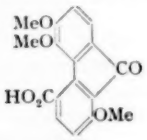
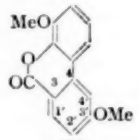
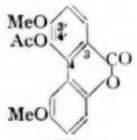

(VIII)

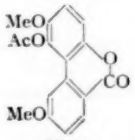
loc. cit., 1905, but wrongly analysed and stated to be optically inactive), which was racemised by heat. The heat treatment also caused some polymerisation (of the styrene system?) to occur, a very sparingly soluble substance, of molecular weight >5000, being obtained. Oxidation of (V) with potassium permanganate in acetone afforded 5 : 6 : 5′-trimethoxydiphenic acid (VI; R = Me) and the corresponding dialdehyde (VII). The latter (which could be oxidised to the former) was also obtained, together with benzaldehyde, by the ozonolysis of (V).

5 : 6 : 5′-Trimethoxydiphenic acid was synthesised in stages from 4-acetoxy-3 : 6-dimethoxyphenanthrenequinone (acetylthebaolquinone; Freund and Göbel, *Ber.*, 1897, **30**, 1389) (VIII). This was oxidised by hydrogen peroxide in hot glacial acetic acid to 6-acetoxy-5 : 5′-dimethoxydiphenic acid (VI; R = Ac), which on hydrolysis yielded 6-hydroxy-5 : 5′-dimethoxydiphenic acid (VI; R = H); and thence on methylation 5 : 6 : 5′-trimethoxydiphenic acid (VI; R = Me). This acid and 1 : 5 : 6-trimethoxyfluorenone-4-carboxylic acid (IX), obtained by heating (VI; R = Me) with concentrated


(IX)


(X)


(XI)

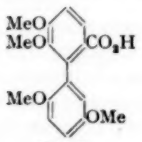

(XII)

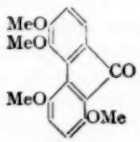
sulphuric acid at 50°, were identified by mixed melting points with the corresponding derivatives from the oxidation of (V). Attempts to convert (VI; R = Ac) into a fluorenonecarboxylic acid by treatment with sulphuric acid resulted in hydrolysis and decarboxylation, the product being 8 : 3′-dimethoxy-3 : 4-benzocoumarin (X), also obtained in the same way from (VI; R = H).

The hydrogen peroxide oxidation of acetylthebaolquinone yielded, in addition to (VI; R = Ac), a lactone shown to be 4′-acetoxy-6 : 3′-dimethoxy-3 : 4-benzocoumarin (XI) and not the isomeride (XII), by hydrolysis to 4′-hydroxy-6 : 3′-dimethoxy-3 : 4-benzocoumarin and hydrolysis and methylation of the latter to 5 : 6 : 2′ : 5′-tetramethoxydiphenyl-2-carboxylic acid (XIII). The acid chloride of this on cyclisation with stannic chloride afforded 1 : 4 : 5 : 6-tetramethoxyfluorenone (XIV) together with a small amount of a by-product, also obtained as the only isolable product from the cyclisation with aluminium chloride and believed to be 1 : 6-dihydroxy-4 : 5-dimethoxyfluorenone (XV) formed by demethylation of the *o*- and *p*-methoxy-groups in (XIV).

Ample verification of the structure (II) for phenyldihydrothebaine is afforded by these degradations and in most cases the constitutions of the derivatives follow readily from (II). Those in which the vinyl group produced during exhaustive methylation has undergone

cyclisation with the phenolic hydroxyl require special mention. As the aromatic nuclei in these must be virtually coplanar the restricted rotation isomerism would be expected to vanish, and indeed in the phenyldihydrothebaine series all the nitrogen-free cyclised


(XIII)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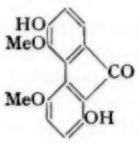
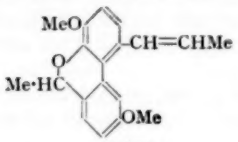
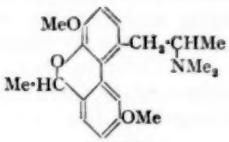
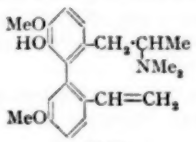

(XV)

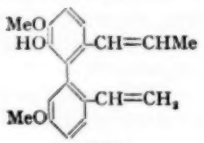
products (containing no asymmetric carbon atom) are inactive. However, in the methyldihydrothebaine series a small optical activity (*ca.* 9°) has been observed for (XVI) (Small and Fry, *loc. cit.*)

As the optically active forms of (XVI) were obtained by degradation of (XVII), and this in turn was prepared by cyclisation of (XVIII), the explanation of the phenomenon is


(XVI)

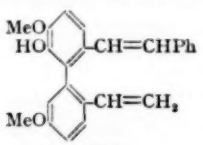

(XVII)

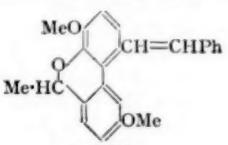

(XVIII)

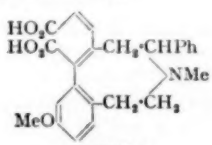

(XIX)

doubtless that the presence of an asymmetric carbon atom in the latter caused production of unequal amounts of the two diastereoisomers of (XVII) when the new asymmetric carbon atom was brought into being as a result of the cyclisation The effect of a slight excess of one diastereoisomer when degradation was pursued to the nitrogen-free product (XVI) would be to cause the latter to have a slight optical activity.

It is of interest that the two unsaturated groups in the uncyclised nitrogen-free product (XIX) of degradation of the methyldihydrothebaines are probably too small to cause restriction of complete rotation of the two phenyl nuclei, and indeed no convincing evidence has been produced to show that (XIX) has been obtained in an optically active form. The activity of the liquid product of degradation of δ-methyldihydrothebaine methine methyl ether is probably due to regeneration of some of the methine base (known to be active) from the quaternary salt. The "ethylphenylhexahydrothebaol" prepared by reduction of (XX) (Small, Sargent, and Bralley, *loc. cit.*) is clearly a tetrahydro-compound, and the "phenyl-6-methoxythebenane" prepared by the reduction of (XXI) (Small, Sargent, and Bralley) is clearly an octahydro-derivative arising from saturation of the double bond and external phenyl group, the analytical data agreeing better with these formulæ than with those allotted to them by Small, Sargent, and Bralley.


(XX)


(XXI)

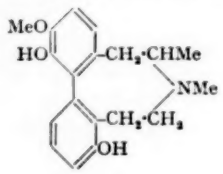

(XXII)

The first stage of the Hofmann degradation of phenyldihydrothebaine affords a methine and an *iso*methine, the former being a stilbene and the latter a styrene. The formation of the isomerides is dependent on the direction of elimination in the methohydroxide of (II). Now the *iso*methine is obtained in the larger relative amount and this means that $\rangle$—CH_2·CH_2·NR_3^+ ⟶ $\rangle$—CH:CH_2 is preferred to $\rangle$—CH_2·CHPh·NR_3^+ ⟶ $\rangle$—CH:CHPh. Fieser and Fieser (*op. cit.*) comment on this and see no explanation for the predominant elimination towards the group not under the influence of the introduced phenyl group. However, it is a proton in the β-position to NR_4^+ which is removed to initiate the elimination and this is not directly activated by the newly introduced phenyl

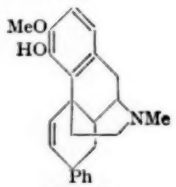
group. Apart from this circumstance the two sides of the basic nitrogen atom are not symmetrically situated in that one leads to a catechol nucleus and the other to a phenol nucleus. We are hardly able at this stage to prognosticate the activation effects in this complex system.

Phenyldihydrothebaine on treatment with hydrogen peroxide and hydrochloric acid yields a dichloro-compound which has been degraded to a nitrogen-free product. Freund and Holtoff (*loc. cit.*) regarded this as formed by addition of chlorine to a double bond, but the analytical data for all the derivatives are equally compatible with formulæ containing two less hydrogen atoms, and it is clear that the two chlorine atoms have entered either the guaiacol or the anisole nucleus, or both nuclei. The reaction with bromine doubtless takes a similar course, yielding dibromophenyldihydrothebaine; this is reported by Freund and Holtoff to undergo electrolytic reduction with production of "phenyltetrahydrothebaine," which is very probably (+)-α-phenyldihydrothebaine, the melting points of the methiodides of these two compounds differing by only one degree. The small amount of (+)-δ-isomer, doubtless present in Freund and Holtoff's phenyldihydrothebaine, would be eliminated by the several crystallisations during this cycle of reactions. The reaction between phenyldihydrothebaine and hydrogen peroxide in boiling alkali yields a dibasic acid, $C_{24}H_{25}O_5N$ (Freund and Holtoff), for which structure (XXII) is now suggested.

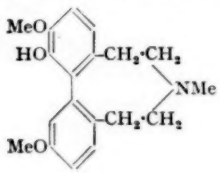
With regard to the other anomalous products of the Grignard reaction, methyldihydro-ψ-codeinone (Small and Lutz, *J. Amer. Chem. Soc.*, 1935, **57**, 2651) is clearly (XXIII).



(XXIII)



(XXIV)

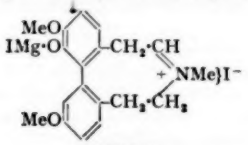


(XXV)

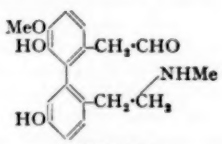
The analytical data for phenyldihydrodeoxycodeine-C were interpreted by Small and Yuen (*ibid.*, 1936, **58**, 192) as agreeing with (XXIV) $C_{24}H_{27}O_2N$, but they are equally compatible with $C_{24}H_{29}O_2N$, which could be explained by assuming reduction of the double bond to have occurred during the reaction with the Grignard reagent, an unusual, but not altogether impossible, reaction. If this explanation is correct then the resistance of the base to hydrogenation is not surprising, and the absorption of four moles of hydrogen when the reaction is forced can be explained by assuming reductive scission of the nitrogen ring and saturation of the phenyl group. If methyldihydro-ψ-codeine methyl ether (Small, Turnbull, and Fitch, *J. Org. Chem.*, 1938, **3**, 204) has a structure analogous to (XXIII) it should contain two hydrogen atoms less than reported by its discoverers, and in this connection it is of interest to note that its production in *iso*propyl ether was reported to be accompanied by the production of a substance giving analytical figures for, and no melting-point depression with, tetrahydro-ψ-codeine methyl ether.

Attempts have been made to prepare the unsubstituted "dihydrothebaine" (XXV), but these have not so far met with success. On the assumption that the conversion of thebaine into phenyldihydrothebaine is initiated by the attack of the thebaine cyclic-ether oxygen atom by $MgBr^+$ the reaction between thebaine and anhydrous magnesium iodide was investigated. This was found to give a light brown solid that contained no thebaine, and that degenerated rapidly on exposure to moist air, but was shown to contain magnesium and iodine. The structure (XXVI) is possible for this substance, though no 4-methoxyphthalic acid was obtained by oxidising it with permanganate. (XXVI) differs little from the thebenine precursor (XXVII) suggested by Gulland and Robinson (*J.*, 1923, 980), and boiling this compound with dilute hydrochloric acid gave a substance having a fluorescence indistinguishable from that of thebenine in acid solution, but markedly different in alkali was obtained. Complete methylation of this acid-treatment product and

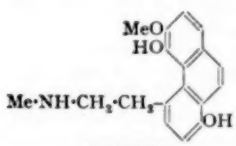
chromatographic analysis of the resulting material afforded no identifiable substance, whilst thebenine (XXVIII) under the same conditions gave a good yield of the dimethyl ether quaternary methosulphate.



(XXVI)

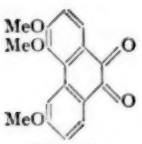


(XXVII)

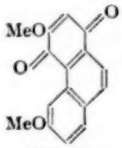


(XXVIII)

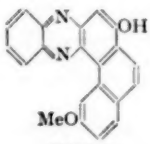
Reduction of the thebaine–magnesium iodide product with lithium aluminium hydride proceeds rapidly with evolution of gas (methane) and production of what appears to be a phenolic secondary amine that has so far defied all attempts to convert it into crystalline derivatives. If this substance is the *N*-demethylated derivative of (XXV) its non-crystalline nature could possibly be explained by assuming that it is a mixture of isomers, as examination of models shows that with no substituent on the nine-membered ring racemisation would be easy. The lithium aluminium hydride reduction of Schiff's base methiodides has been shown to give rise to secondary amines (Forbes, private communication). In spite of the unpromising nature of these results it is hoped to pursue this reaction further. The sodium–ammonia reduction of this substance yields an intractable phenolic base, whilst phenyldihydrothebaine was obtained by treating it with phenylmagnesium bromide. This last result encourages us in the belief that this substance (naturally the related bromide) is an intermediate in the production of phenyldihydrothebaine.



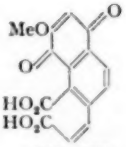
(XXIX)



(XXX)



(XXXI)



(XXXII)

Oxidation of 3 : 4 : 6-trimethoxyphenanthrene by chromic acid in an attempt to prepare the 9 : 10-quinone (XXIX) led surprisingly to 3 : 6-dimethoxyphenanthra-1 : 4-quinone (XXX), identified by condensation with *o*-phenylenediamine to 3-hydroxy-7′-methoxynaphtho(1′ : 2′-1 : 2)phenazine (XXXI), which was alkali-soluble, by hydrogen peroxide oxidation to 8-carboxy-7-2′-carboxyvinyl-2-methoxy-1 : 4-naphthaquinone (XXXII), and by permanganate oxidation to benzene-1 : 2 : 3 : 4-tetracarboxylic acid. Structure (XXX) for the quinone was finally confirmed by its production by oxidation of 4-hydroxy-3 : 6-dimethoxyphenanthrene (thebaol) with chromic acid.

Experimental

(All m. p.s are uncorrected.)

Oxidation of Phenyldihydrothebaine.—A warm solution of potassium permanganate (75 g.) in water (1 l.) was added during 2 hours to a stirred solution of phenyldihydrothebaine perchlorate (15 g.) in 2N-sodium hydroxide (100 ml.). A considerable quantity of benzaldehyde was produced during the oxidation. When all the permanganate had been added the mixture was heated on the steam-bath for 2 hours, then filtered, and the residue washed three times with boiling water. The filtrate and washings were nearly neutralised with hydrochloric acid, concentrated to a small bulk, filtered, and acidified with hydrochloric acid. The precipitate (A) was collected and the filtrate (B) set aside (see below). The solid (A) was extracted three times with boiling water, and the hot extract boiled with animal charcoal, filtered, and allowed to cool. Benzoic acid, identified by mixed m. p. with an authentic specimen, was deposited from the solution. The residue from this extraction was warmed with sodium hydrogen carbonate solution, leaving an intractable tar. The carbonate solution was boiled with charcoal, cooled, and acidified with hydrochloric acid, and in this way a pale brown-grey solid (? IV) was obtained. This could not be crystallised but was converted into the *copper* derivative

by addition of a solution of copper acetate in methanol to a solution of the acid in methanol. The copper derivative was extremely sparingly soluble in all solvents, and decomposed without melting above 250° (Found : C, 51·2; H, 4·51; Cu, 12·8. $C_{20}H_{18}O_6NCu,2H_2O$ requires C, 51·2; H, 4·9; Cu, 13·5. Found, after drying at 100°/0·1 mm.: C, 53·4; H, 4·4; Cu, 12·6. $C_{20}H_{18}O_6NCu,H_2O$ requires C, 53·2; H, 4·6; Cu, 14·1%).

All attempts to purify the acid or prepare other derivatives failed.

The filtrate (B) was saturated with ammonium sulphate and extracted eighteen times with ether, and the combined extracts were dried (Na_2SO_4) and evaporated. The syrupy residue partly crystallised when kept overnight in the refrigerator. It was triturated with chloroform, and the solid collected (2·1 g.). This substance afforded a fluorescein in the usual way, and on recrystallisation from boiling water was obtained as pale yellow needles, m. p. *ca.* 170° (rapid heating) undepressed on admixture with an authentic specimen of 4-methoxyphthalic acid (Found : C, 55·1; H, 4·0. Calc. for $C_9H_8O_5$: C, 55·1; H, 4·1%). The anhydride separated from benzene–light petroleum as bunches of pale yellow needles, m. p. 94° undepressed by addition of an authentic specimen (Found : C, 61·0; H, 3·2. Calc. for $C_9H_6O_4$: C, 60·7; H, 3·4%). The methylimide, prepared by evaporating a solution of the acid in aqueous methylamine and distilling the residue, crystallised from alcohol, as bunches of long, slender, very pale yellow needles, m. p. 156°, undepressed by admixture with an authentic specimen (Found : C, 62·8; H, 4·6; N, 6·8. Calc. for $C_{10}H_9O_3N$: C, 62·8; H, 4·7; N, 7·3%).

(+)-α-*Phenyldihydrothebaine Methyl Ether.*—Methyl sulphate (3·08 ml., 4·08 g.) in methyl alcohol (8 ml.) was slowly added to a solution of (+)-α-phenyldihydrothebaine hydrochloride (7 g.) in 10% aqueous sodium hydroxide (100 ml.) with constant shaking. The solid that separated as the reaction proceeded was collected, and dissolved in warm dilute perchloric acid. (+)-α-*Phenyldihydrothebaine methyl ether perchlorate* crystallised on cooling, and was obtained as colourless plates, m. p. 205°, on recrystallisation from alcohol, $[\alpha]_D^{21}$ +9·26° (in water) (Found : C, 62·2; H, 6·1; Cl, 6·7. $C_{26}H_{19}O_3N,HClO_4$ requires C, 62·0; H, 6·0; Cl, 7·0%). The *methiodide*, obtained by boiling the free base in methanol with methyl iodide, formed large colourless prisms, m. p. 205° after recrystallisation from alcohol (Found : C, 59·5; H, 5·9; N, 2·8; I, 22·5. $C_{27}H_{32}O_3NI$ requires C, 59·4; H, 5·9; N, 2·6; I, 22·3%).

(+)-α-Phenyldihydrothebaine methine methyl ether was prepared as directed by Freund (*Ber.*, 1905, **38**, 3252).

(+)-3 : 4-*Dimethoxy*-2-(5-*methoxy*-2-*vinylphenyl*)*stilbene* (V).—A solution of sodium (12·5 g.) in methanol (250 ml.) was added to one of (+)-α-phenyldihydrothebaine methine methyl ether methiodide (from 21 g. of the base) in methanol (100 ml.), and the mixture refluxed for 2 hours, then poured into water, and the resulting suspension saturated with ammonium chloride and extracted with ether (3 × 250 ml.). The combined extracts were shaken with 2N-hydrochloric acid (3 × 25 ml.), washed well with water, and dried (Na_2SO_4), and the ether was removed. The crystalline residue (15 g.) was recrystallised from alcohol; it was obtained as very large, colourless prisms, m. p. 115°, $[\alpha]_D^{18}$ +59° (*c*, 2 in acetone) (Found : C, 80·3; H, 6·3; OMe 24·1. $C_{25}H_{24}O_3$ requires C, 80·6; H, 6·4; OMe, 24·9%). On being heated at 130° for 10 minutes it was converted into the *racemate*, obtained as colourless prisms, m. p. 124°, $[\alpha]_D^{17}$ 0·0° (in acetone), after recrystallisation from alcohol (Found : C, 80·1; H, 6·4%). In addition, a very sparingly soluble amorphous *polymer*, which had no definite m. p., was obtained after this heat treatment [Found : C, 80·4; H, 6·9%; *M* (in camphor), >5000].

(+)-2-(2-*Ethyl*-5-*methoxyphenyl*)-3 : 4-*dimethoxydibenzyl.*—(+)-3 : 4-Dimethoxy-2-(5-methoxy-2-vinylphenyl)stilbene (2 g.) was shaken under hydrogen at 3 atm. in ethyl acetate (50 ml.) in presence of the Raney nickel catalyst. The filtered solution was evaporated and the residual *dibenzyl*, which could not be crystallised, had b. p. 220°/0·1 mm., $[\alpha]_D^{18}$ +3·5° (in alcohol) (Found : C, 79·5; H, 7·8. $C_{25}H_{28}O_3$ requires C, 79·8; H, 7·5%). Partial racemisation probably occurred during the distillation; there was no evidence of the production of a hexahydro-derivative under these conditions.

Oxidation of (+)-3 : 4-*Dimethoxy*-2-(5-*methoxy*-2-*vinylphenyl*)*stilbene.*—Potassium permanganate (4·25 g.) in warm acetone (350 ml.) was added during 1·5 hours to a warm stirred solution of (+)-3 : 4-dimethoxy-2-(5-methoxy-2-vinylphenyl)stilbene (1·7 g.) in acetone (25 ml.). The mixture was kept for 15 minutes, the acetone removed by distillation, the residue warmed with dilute sodium carbonate solution and filtered, and the residue washed well with sodium carbonate solution and ether. The combined filtrates were extracted twice with 30-ml. portions of ether, the combined ethereal extracts and residue washings were dried (Na_2SO_4), and the ether was removed by distillation, leaving a viscous oil. This gave the *bis*-2 : 4-*dinitrophenylhydrazone* of 2 : 2′-diformyl-5 : 6 : 5′-trimethoxydiphenyl on being warmed

with 2 : 4-dinitrophenylhydrazine in alcoholic sulphuric acid. The derivative (of VII) was obtained as orange-red, rhombic plates, m. p. 277° after recrystallisation from dioxan (Found : C, 53·0; H, 3·6; N, 16·3. $C_{29}H_{24}O_{11}N_8$ requires C, 52·7; H, 3·6; N, 16·9%).

The sodium carbonate solution, after extraction with ether, was concentrated to a small bulk, cooled in ice-water, and acidified with ice-cold hydrochloric acid. The solid mass that separated was resinous at the room temperature, but crystallised on trituration with aqueous methanol. In this manner 5 : 6 : 5′-*trimethoxydiphenic acid* (VI; R = Me) was obtained, and recrystallised as minute, colourless, slender prisms, m. p. 215°, from aqueous methanol, $[\alpha]_D^{19}$ 0° (Found : C, 61·5; H, 5·2. $C_{17}H_{16}O_7$ requires C, 61·4; H, 4·8%).

5 : 6 : 5′-Trimethoxydiphenic acid, heated with concentrated sulphuric acid at 50° for 30 minutes, was converted into 1 : 5 : 6-*trimethoxyfluorenone*-4-*carboxylic acid* (IX), which was obtained as a yellow solid when the mixture was poured into water; fine yellow needles, m. p. 256°, were obtained on recrystallisation from 50% acetic acid (Found : C, 64·7; H, 4·2. $C_{17}H_{14}O_6$ requires C, 65·0; H, 4·5%). The fluorenone was readily soluble in aqueous sodium carbonate; its 2 : 4-*dinitrophenylhydrazone* was obtained as a dark red amorphous powder, m. p. 286°, on attempted recrystallisation from dioxan–light petroleum (Found : N, 11·3. $C_{23}H_{18}O_9N_4$ requires N, 11·3%).

Conversion of *Acetylthebaol into* 5 : 6 : 5′-*Trimethoxydiphenic Acid.*—4-Acetoxy-3 : 6-dimethoxyphenanthraquinone (acetylthebaolquinone) was prepared by the oxidation of acetylthebaol with chromic acid (Freund and Göbel, *loc. cit.*). It was found advisable to carry out the oxidation in cold acetic acid rather than in hot. The product was obtained as long, bright yellow needles, m. p. 205° after crystallisation from acetic acid (Found : C, 65·9; H, 4·5. Calc. for $C_{18}H_{14}O_6$: C, 66·2; H, 4·3%). The related *phenazine* derivative was prepared by condensation of the quinone with *o*-phenylenediamine in acetic acid, and crystallised from nitrobenzene as minute, yellow prisms, m. p. 265° (Found : C, 72·0; H, 4·7; N, 7·1. $C_{24}H_{16}O_4N_2$ requires C, 72·4; H, 4·5; N, 7·0%).

4-Acetoxy-3 : 6-dimethoxyphenanthraquinone (10 g.) was dissolved in hot acetic acid (120 ml.), mixed with 30% hydrogen peroxide (16 ml.), and kept for 2 hours at 70—80°. Further hydrogen peroxide (16 ml.) was then added and the mixture heated for 5 hours at 100°. Next day the liquid was heated on the steam-bath, and water slowly added to incipient precipitation; on cooling, a quantity of crystalline material separated. This was collected and found to consist mainly of by-products (see below). The filtrate was further diluted until the total volume was approx. 1700 ml., and set aside overnight in the refrigerator, whereupon 6-*acetoxy*-5 : 5′-*dimethoxydiphenic acid* (VI; R = Ac) (5 g.) separated. This was collected, washed, and dissolved in dilute sodium hydrogen carbonate solution, and the solution was filtered and acidified with hydrochloric acid, the acid separating as a mass of fine needles. It crystallised from aqueous alcohol in long, slender, colourless needles, m. p. 229° (Found : C, 58·6; H, 4·5. $C_{18}H_{16}O_8,0{\cdot}5H_2O$ requires C, 58·5; H, 4·6%).

When a solution of the acid in concentrated sulphuric acid was heated at 50° for 30 minutes and diluted with water, a light brown solid separated. This proved to be 8 : 3′-*dimethoxy*-3 : 4-*benzocoumarin* (X), and was obtained as long, slender, almost colourless needles, m. p. 148—149°, by recrystallisation from alcohol (Found : C, 70·0; H, 4·7. $C_{18}H_{12}O_4$ requires C, 70·3; H, 4·7%). This substance showed no ketonic properties, and dissolved in sodium hydroxide solution only on prolonged boiling.

6-Acetoxy-5 : 5′-dimethoxydiphenic acid (1·5 g.) was heated on the steam-bath with 20% aqueous sodium hydroxide (15 ml.) for 2 hours, and the solution cooled in ice and acidified with ice-cold hydrochloric acid. The solid that separated was collected, washed with water, and recrystallised from 50% aqueous alcohol, whereupon 6-*hydroxy*-5 : 5′-*dimethoxydiphenic acid* (VI; R = H) was obtained as colourless prisms, m. p. 172° with effervescence (lactone formation ?), resolidification, and remelting at 235° (Found, in material dried at 100°/15 mm. : C, 60·0; H, 3·9. $C_{16}H_{14}O_7$ requires C, 60·3; H, 4·4. Found, in material dried at 190°/0·01 mm. : C, 64·3; H, 4·0. $C_{16}H_{12}O_6$ requires C, 64·0; H, 4·0%). The acid was readily soluble in sodium hydrogen carbonate solution and in alcohol; its alcoholic solution gave no colour on addition of ferric chloride.

When heated with concentrated sulphuric acid at 50° for 30 minutes this acid was converted into 8 : 3′-dimethoxy-3 : 4-benzocoumarin, m. p. 148—149°, identical with the substance obtained in the same way from the 6-acetoxy-acid.

6-Hydroxy-5 : 5′-dimethoxydiphenic acid (1 g.) was dissolved in 20% aqueous sodium hydroxide (20 ml.), and methyl sulphate (1·78 ml., 2·25 g.) slowly added with constant shaking. The mixture was then heated on the steam-bath for an hour, cooled in ice, and acidified with

ice-cold hydrochloric acid. 5 : 6 : 6′-Trimethoxydiphenic acid (VI; R = Me) separated as a semi-solid mass, and was obtained as colourless prisms, m. p. 213—214°, by crystallisation from aqueous alcohol. Recrystallised, it had m. p. 215°, undepressed by admixture with the acid obtained by oxidation of (+)-3 : 4-dimethoxy-2-(5-methoxy-2-vinylphenyl)stilbene. The acid, when heated for 30 minutes at 50° with concentrated sulphuric acid, was converted into 1 : 5 : 6-trimethoxyfluorenone-4-carboxylic acid, m. p. 256° undepressed on mixing with the specimen obtained from the degradation product.

The By-product of the Oxidation of 4-*Acetoxy*-3 : 6-*dimethoxyphenanthraquinone.*—The solid first separating from the products of oxidation of acetylthebaolquinone (see above) was shaken with dilute sodium carbonate solution, and the insoluble matter collected. Acidification of the filtrate yielded a small amount of 6-acetoxy-5 : 5′-dimethoxydiphenic acid. The residue was only slowly soluble in boiling sodium hydroxide solution, and was reprecipitated unchanged on acidification. It was obtained as bunches of very long, very pale brown needles, m. p. 192°, on recrystallisation from alcohol, and is regarded as 4′-*acetoxy*-6 : 3′-*dimethoxy*-3 : 4-*benzocoumarin* (XI) (Found : C, 64·8; H, 4·3. $C_{17}H_{14}O_6$ requires C, 64·9; H, 4·5%). A solution of this substance (7 g.) in alcohol (140 ml.) was refluxed for 4 hours with 20% alcoholic potassium hydroxide (31 ml.), with the addition of just sufficient 30% hydrogen peroxide to convert the dark brown solution to a pale straw colour. The mixture was cooled and acidified with ice-cold hydrochloric acid. The precipitated solid was collected and crystallised from alcohol, 4′-*hydroxy*-6 : 3′-*dimethoxy*-3 : 4-*benzocoumarin* being obtained as pale pink prisms, m. p. 172° (Found : C, 65·7; H, 4·4. $C_{15}H_{12}O_5$ requires C, 66·1; H, 4·4%). The substance is soluble in aqueous sodium hydroxide, but insoluble in sodium carbonate. Its alcoholic solution gives an intense blue colour with ferric chloride. The result of the hydrolysis was the same when no hydrogen peroxide was added, though in this case the product was much darker.

4′-Hydroxy-6 : 3′-dimethoxy-3 : 4-benzocoumarin (5 g.) was boiled with 10% aqueous potassium hydroxide (103 ml.), and methyl sulphate (16·9 ml., 22·3 g.) added during 2 hours with mechanical stirring. Potassium hydroxide (5 g.) was added and the solution boiled for ½ hour more, cooled, and acidified with hydrochloric acid, whereupon a gummy precipitate separated. This was obtained crystalline on trituration with aqueous alcohol, and the solid collected (4·1 g.). 5 : 6 : 2′ : 5′-*Tetramethoxydiphenyl*-2-*carboxylic acid* (XIII) was obtained as slender colourless needles, m. p. 162·5°, on recrystallisation from alcohol (Found : C, 63·8; H, 5·5. $C_{17}H_{18}O_6$ requires C, 64·1; H, 5·6%). The red solution in concentrated sulphuric acid, after being heated at 50° for 30 minutes, gave no precipitate on dilution with water.

Cyclisation of 5 : 6 : 2′ : 5′-*Tetramethoxydiphenyl*-2-*carboxylic Acid.*—(*a*) The acid was recovered mainly unchanged after 2 hours' heating on the steam-bath with syrupy phosphoric acid and phosphoric oxide.

(*b*) 5 : 6 : 2′ : 5′-Tetramethoxydiphenyl-2-carboxylic acid (1 g.) was converted into the acid chloride by boiling it with thionyl chloride (2 ml.) for 30 minutes. After removal of the excess of thionyl chloride, the acid chloride was dissolved in carbon disulphide, and the mixture heated under reflux with aluminium chloride (0·85 g.) until evolution of hydrogen chloride ceased. The carbon disulphide was removed by distillation and the residue decomposed by ice-water and hydrochloric acid, giving a gummy orange mass. This dissolved in hot alcohol, to give an intensely coloured solution, from which on cooling a quantity of light brown solid separated. This was collected and 1 : 6-*dihydroxy*-4 : 5-*dimethoxyfluorenone* (XV) (or an isomer) was obtained as colourless needles, m. p. 147° (Found : C, 66·4; H, 4·6. $C_{15}H_{12}O_5$ requires C, 66·1; H, 4·4%). The substance was readily soluble in aqueous sodium hydroxide, insoluble in aqueous sodium carbonate. Its alcoholic solution gave an intense green colour with ferric chloride. No definite substance could be obtained from the mother liquors of the crystallisation of this compound, though not all the material in these was soluble in alkali.

(*c*) Phosphorus pentachloride (0·83 g.) was added to a suspension of the tetramethoxydiphenylcarboxylic acid (1·2 g.) in dry benzene (10 ml.), and the mixture warmed on the steam-bath until conversion into the acid chloride was complete. It was then cooled in ice-water until crystallisation of the benzene began, and anhydrous stannic chloride (1·95 g.) in benzene (5 ml.) added. A dark violet solid separated. The mixture was kept at the room temperature for 6 hours; ice-water, hydrochloric acid, and ether were added, a bright orange solid then separating. The organic solvents were removed and the solid was collected (1·1 g.), washed well with water and crystallised from alcohol. A crop of stout yellow prisms was first obtained, followed by a much smaller crop of pale yellow needles. The prisms were recrystallised from alcohol, 1 : 4 : 5 : 6-*tetramethoxyfluorenone* (XIV) being obtained as bright yellow prisms, m. p. 183° (Found : C, 68·0; H, 5·4. $C_{17}H_{16}O_5$ requires C, 68·0; H, 5·3%). This substance was

insoluble in alkali, and its alcoholic solution gave no colour with ferric chloride. Its dilute solutions exhibited an intense yellow fluorescence. The 2 : 4-*dinitrophenylhydrazone* was obtained as bunches of bright red needles, m. p. 290°, on recrystallisation from nitrobenzene (Found : C, 57·7; H, 4·0; N, 11·6. $C_{23}H_{20}O_8N_4$ requires C, 57·5; H, 4·2; N, 11·7%).

The needles obtained during the first crystallisation of the ketone were separated from the prisms, first by hand-picking, and then by repeated crystallisation from alcohol, being then obtained as almost colourless needles, m. p. 146°, undepressed on admixture with the product of the aluminium chloride cyclisation (*b* above) (Found : C, 66·1; H, 4·9%). The 2 : 4-*dinitrophenylhydrazone* from this compound had m. p. 285° after crystallisation from glacial acetic acid (Found : N, 12·3. $C_{21}H_{16}O_8N_4$ requires N, 12·4%).

Ozonolysis of (+)-3 : 4-*Dimethoxy*-2-(5-*methoxy*-2-*vinylphenyl*)*stilbene*.—Ozonised oxygen was passed through a solution of (+)-3 : 4-dimethoxy-2-(5-methoxy-2-vinylphenyl)stilbene (5·3 g.) in dry chloroform (30 ml.) cooled in ice-water, until a test portion no longer decolorised a carbon tetrachloride solution of bromine. The chloroform was removed by distillation, and the ozonide reduced by the addition of glacial acetic acid (20 ml.), ether (30 ml.), water (0·2 ml.), and zinc dust (5 g.). When the initial vigorous reaction had subsided the mixture was refluxed until a test portion no longer gave a colour with starch–potassium iodide paper; it was then filtered from solid matter and the residue washed well with ether. The filtrate and ethereal washings were collected, the ethereal layer was separated, and the aqueous layer extracted twice with ether. The combined ethereal extracts were washed, dried, and evaporated, leaving a brown oil smelling strongly of benzaldehyde. This was extracted three times with boiling light petroleum (b. p. 80—100°). The residue could not be crystallised but gave the bis-2 :4-dinitrophenylhydrazone of 2 : 2′-diformyl-5 : 6 : 5′-trimethoxydiphenyl on treatment with dinitrophenylhydrazine in alcoholic sulphuric acid. The derivative was obtained as orange-red plates, m. p. 277°, undepressed by admixture with a specimen of the 2 : 4-dinitrophenylhydrazone obtained from the product of potassium permanganate oxidation of this nitrogen-free substance. The parent *aldehyde* was obtained as a viscous light brown oil (2 g.), b. p. 215—219° (bath-temp.)/0·3 mm. (Found : C, 67·5; H, 5·6. $C_{17}H_{16}O_5$ requires C, 68·0; H, 5·3%).

The light petroleum extract, on cooling, deposited some of this aldehyde, and on decantation and evaporation of the solution, a small amount of benzaldehyde was obtained and identified by its odour and by preparation of its 2 : 4-dinitrophenylhydrazone, m. p. 236°.

On one occasion only, the residue from the light petroleum extract yielded a small amount of colourless prisms, m. p. 147°, from benzene (charcoal), becoming yellow on exposure to air (Found : C, 67·4; H, 5·3. $C_{17}H_{16}O_5$ requires C, 68·0; H, 5·3). This substance was devoid of ketonic properties; it dissolved in boiling aqueous sodium hydroxide, and was precipitated on acidification. It may possibly be the *lactone* of 5 : 6 : 5′-trimethoxy-2′(? 2)-hydroxymethyl-diphenyl-2(? 2′)-carboxylic acid produced by Cannizzaro reaction of the aldehyde.

Oxidation of 2 : 2′-*Diformyl*-5 : 6 : 5′-*trimethoxydiphenyl*.—Potassium permanganate (1·2 g.) in warm water (30 ml.) was slowly added to a stirred suspension of the dialdehyde (1·6 g.) in water (50 ml.) at 70° with passage of carbon dioxide. The mixture was heated at 70° for 30 minutes after the appearance of a permanent violet colour, and filtered from solid matter, which was washed with water, and the colour of the filtrate discharged by sulphur dioxide, whereupon 5 : 6 : 5′-trimethoxydiphenic acid was precipitated as a gummy solid. This was obtained, after three crystallisations from aqueous alcohol, as colourless prisms, m. p. 215°, undepressed by admixture with an authentic specimen.

2 : 2′-Diformyl-5 : 6 : 5′-trimethoxydiphenyl was converted into a black tar when heated at 100° with 25% aqueous sodium hydroxide; it was recovered unchanged after treatment with cold alkali, and also after being heated on the steam-bath for 24 hours with malonic acid and pyridine.

Reaction between Thebaine and Anhydrous Magnesium Iodide.—A solution of anhydrous magnesium iodide (5 g.) in dry benzene (40 ml.) and dry ether (10 ml.) was added during an hour to a boiling, vigorously stirred solution of thebaine (5 g.) in benzene (100 ml.). A black-green precipitate formed at once, this colour quickly changing to green, and to light brown after 4 hours' boiling. No further change in colour was noted though the mixture was boiled for 36 hours. The brown solid was collected, washed well with hot benzene and ether, and kept in a vacuum-desiccator. It rapidly degenerated to a black-brown substance when kept in moist air, and slowly to a greenish-grey substance on prolonged storage *in vacuo*. On treatment with water a substance was obtained that was soluble in alkali and gave an intense red colour with diazobenzenesulphonic acid, but this could not be crystallised, nor could any crystalline derivative be prepared.

On 3 minutes' boiling with 15% hydrochloric acid the thebaine–magnesium iodide product was converted into a gum, obtained on cooling the solution. This was found to have a fluorescence in acid media indistinguishable from that of thebenine, but the fluorescence of the two in alkali was markedly different. The gum was fully methylated by methyl sulphate and alkali, the product dissolved in benzene–chloroform, and the solution passed down a column of alumina. No band could be distinguished. Thebenine, when methylated and chromatographed in the same way, gave a bright green fluorescent band, that on elution proved to contain *NN*-dimethylthebenine *OO*-dimethyl ether methosulphate, obtained as minute colourless prisms, m. p. 280°, on recrystallisation from alcohol (Found: C, 59·4; H, 6·7; N, 3·0. Calc. for $C_{22}H_{28}O_3N,CH_3SO_4$: C, 59·3; H, 6·7; N, 3·0%).

The thebaine–magnesium iodide reaction product (8 g.) was oxidised in the same way as phenyldihydrothebaine, but no identifiable acid could be isolated, nor any that gave a fluorescein derivative on fusion with resorcinol and a trace of concentrated sulphuric acid.

Reaction between the Thebaine–Magnesium Iodide Product and Phenylmagnesium Bromide.—The thebaine–magnesium iodide reaction product (2 g.) was shaken with excess of phenylmagnesium bromide in dry benzene (40 ml.) for 24 hours at room temperature, the solution poured into excess of saturated aqueous ammonium chloride, and the benzene layer removed. The aqueous portion was extracted with benzene, and the basic substances were removed from the benzene layer with hydrochloric acid. The acid extract was made alkaline with ammonia and the base extracted with ether. On evaporation of the ethereal extract a viscous oil was obtained, and this gave phenyldihydrothebaine perchlorate (0·7 g.) on treatment with aqueous perchloric acid. On recrystallisation from alcohol this had m. p. 245°, undepressed by admixture with (+)-α-phenyldihydrothebaine perchlorate. No search was made for the (+)-δ-phenyldihydrothebaine on this scale.

Reduction of the Thebaine–Magnesium Iodide Product.—(*a*) The reaction product (5 g.) was suspended in liquid ammonia (100 ml.) with stirring, and sodium (0·49 g.) added in thin slices, the blue colour, at first rapidly discharged, finally persisting. The excess of sodium was removed by the addition of a few drops of alcohol, and the solution cautiously poured into water (100 ml.). The precipitate so obtained largely dissolved on the addition of 5 ml. of 10% aqueous sodium hydroxide. The solution was filtered from solid matter, and concentrated hydrochloric acid added drop by drop until precipitation of a near-white solid ceased, the solution remaining strongly alkaline throughout. The precipitate was extracted with chloroform in the presence of sodium dithionite (hydrosulphite), and the extract dried and evaporated to leave a brown gum. This dissolved readily in dilute acids and in alkali, the latter solutions giving an intense red colour with diazobenzenesulphonic acid. The only sparingly soluble derivative obtained from this substance was a *mercuri-iodide* [Found: I, 38·4. $(C_{19}H_{24}O_3N)_2,HgI_4$ requires I, 38·7%. This agreement is possibly fortuitous].

(*b*) Thebaine (10 g.) was treated with anhydrous magnesium iodide (9 g.) in benzene–ether, and the solution boiled under reflux with vigorous stirring throughout the addition of the magnesium iodide and for a further 4 hours. The benzene was largely removed, and dry ether (150 ml.) added, followed slowly by a solution of lithium aluminium hydride (1·5 g.) in ether (220 ml.). A vigorous reaction ensued, gas being evolved and the light brown solid becoming rapidly white. The mixture was stirred and refluxed for a further 1·5 hours, then cooled. A portion of the suspension was shaken with dilute acetic acid, the aqueous layer separated and treated with aqueous sodium perchlorate in the presence of sodium dithionite, whereupon a pale yellow oily perchlorate separated. The aqueous solution was decanted from the gum, which was washed well with water. All attempts to crystallise this perchlorate or to convert it into a crystalline salt failed. Of eighteen different salts of the base investigated, only the perchlorate, salicylate, picrate, and picrolonate were found to be sparingly soluble in water, and all were gums. All the salts were readily soluble in alcohol. The perchlorate, dissolved in hot water, was treated with ammonia in the presence of sodium dithionite; the oily base was precipitated, and proved to be surprisingly sparingly soluble in the usual extracting solvents; it possibly consists of a phenol-betaine. Addition of sodium nitrite solution to a well-cooled acetic acid extract of the original mixture, containing hydrochloric acid, gave an immediate copious orange-red precipitate, from which it is concluded that the base is a secondary amine. Though these results are discouraging it is hoped to investigate this interesting reaction further.

Oxidation of 3 : 4 : 6-*Trimethoxyphenanthrene.*—A solution of chromic acid (12·5 g.) in water (3 ml.) and acetic acid (18 ml.), cooled to −5°, was very cautiously added to a solution of 3 : 4 : 6-trimethoxyphenanthrene (12 g.) in acetic acid (30 ml.) immersed in ice–salt, with constant shaking, during about 1·5 hours. The rate of addition was controlled so that the

temperature did not rise above 30°, otherwise the yield was considerably diminished. After addition of all the chromic acid the mixture was kept in ice for 30 minutes, and then allowed to attain the room temperature. The solid was collected, and washed with glacial acetic acid. **3 : 6-*Dimethoxyphenanthra*-1 : 4-*quinone*** (XXX) was thus obtained as long, orange felted needles, m. p. 220° (4·5 g.); it had m. p. 223° after recrystallisation from glacial acetic acid (Found: C, 71·5, 71·4; H, 4·4, 4·3; OMe, 16·0. $C_{16}H_{12}O_4$ requires C, 71·6; H, 4·5; OMe, 23·1%). It was sparingly soluble in alcohol and readily soluble in acetone. Its solution in concentrated sulphuric acid was deep blue.

A solution of this quinone (0·25 g.) in glacial acetic acid (10 ml.), along with *o*-phenylenediamine (0·25 g.), was heated for 1 hour on the steam-bath. **3-*Hydroxy*-7′-*methoxynaphtho*-(1′ : 2′-1 : 2)*phenazine*** (XXXI) separated as orange felted needles, m. p. 295—297°, sparingly soluble in all solvents (Found: C, 77·0; H, 4·5; N, 8·4; OMe, 8·4. $C_{21}H_{14}O_2N_2$ requires C, 77·3; H, 4·3; H, 8·6; OMe, 9·5. $C_{22}H_{16}O_2N_2$ requires C, 77·6; H, 4·7; H, 8·2; 2OMe, 18·7%). This dissolved readily in warm aqueous alkali, indicating its phenolic nature.

Oxidation of **3 : 6-*Dimethoxyphenanthra*-1 : 4-*quinone***.—Hydrogen peroxide (4 ml.; 30%) was added to a hot solution of 3 : 6-dimethoxyphenanthra-1 : 4-quinone (4 g.) in glacial acetic acid (75 ml.), and the mixture heated on the steam-bath for 19 hours, with the addition of 30% hydrogen peroxide (3 ml.) every 3 hours. The colour first darkened considerably, and then lightened to a pale yellow. The mixture was concentrated to a small bulk, a quantity of solid matter separating from the viscous oily residue. The mixture was triturated with water, the solid collected, washed well with water, and dissolved in aqueous sodium carbonate, and the solution boiled (charcoal), filtered, and acidified. A bright yellow solid separated (0·5 g.). On recrystallisation from aqueous alcohol, **8-*carboxy*-7-2′-*carboxyvinyl*-2-*methoxy*-1 : 4-*naphthaquinone*** (XXXII) was obtained as minute, bright yellow prisms, m. p. 273—275° (decomp.) (Found: C, 58·2; H, 3·3. $C_{15}H_{10}O_7,0{\cdot}5H_2O$ requires C, 57·9; H, 3·5. Found, in material dried at 180°/0·1 mm.: C, 59·4; H, 3·3. $C_{15}H_{10}O_7$ requires C, 59·6; H, 3·3%). The acid was readily soluble in sodium carbonate solution, and this solution readily decolorised potassium permanganate solution.

The major portion of the oxidation product, however, was soluble in water, and was never obtained in a form suitable for analysis. It was oxidised further as follows. The filtrate from the isolation of the solid acid above was made alkaline with sodium hydroxide, and aqueous potassium permanganate added until a permanent violet colour was obtained, whereafter the solution was heated on the steam-bath until all the manganese had been precipitated. The mixture was then filtered, the residue was washed several times with water, and the filtrate and washings were saturated with ammonium sulphate and extracted twenty times with ether. The combined extracts were evaporated, giving a semi-solid mass. This became crystalline on trituration with ethyl acetate, and the solid was collected at the pump. Colourless needles of benzene-**1 : 2 : 3 : 4**-tetracarboxylic acid were obtained by the slow evaporation of its solution in methyl acetate; these had m. p. 242—245° (Bamford and Simonsen, *J.*, 1910, **97**, 1904, give m. p. 238° for this acid) (Found: C, 47·7; H, 2·6. Calc. for $C_{10}H_6O_8$: C, 47·3; H, 2·4%). On fusion with resorcinol and a trace of sulphuric acid this acid gave a substance which exhibited an intense yellow-green fluorescence in alkaline solution. Methyl benzene-1 : 2 : 3 : 4-tetracarboxylate was prepared by the action of methyl iodide on the dry silver salt of the acid, and was obtained as colourless prismatic needles, m. p. 133°, after three recrystallisations from alcohol (Found: C, 54·1; H, 4·7. Calc. for $C_{14}H_{14}O_8$: C, 54·1; H, 4·7%). The crystals became violet on exposure to light. Bamford and Simonsen (*loc. cit.*) give m. p. 133° for this tetramethyl ester.

Oxidation of **4-*Hydroxy*-3 : 6-*dimethoxyphenanthrene*** (*Thebaol*).—Chromic acid (1·9 g.) in water (0·5 ml.) and acetic acid (12 ml.) was slowly added to a solution of thebaol (1·5 g.) (Freund and Göbel, *loc. cit.*) in acetic acid (20 ml.) at the room temperature, with constant shaking, during 10 minutes. The mixture was finally kept at 40° for 10 minutes and then in the refrigerator for 3 hours. The solid that separated was collected, washed with acetic acid, and crystallised from the same solvent, being so obtained as long, slender, orange-red needles (0·4 g.), m. p. 233° alone or mixed with a specimen of 3 : 6-dimethoxyphenanthra-1 : 4-quinone prepared by the oxidation of 3 : 4 : 6-trimethoxyphenanthrene.

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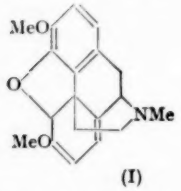
THE DYSON PERRINS LABORATORY, OXFORD UNIVERSITY. [*Received, October* 31*st*, 1951.]

171. *The Reduction of Thebaine and Dihydrothebaine by Sodium and Ammonia.*

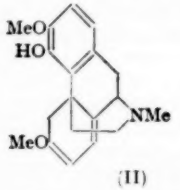
By K. W. Bentley, Sir Robert Robinson, and A. E. Wain.

The sodium–liquid ammonia reduction of thebaine has been shown to give phenolic dihydrothebaine * in excellent yield, and the sodium–liquid ammonia reduction of dihydrothebaine affords dihydrothebainone Δ^5-enol methyl ether. The latter is also obtained by the catalytic reduction of phenolic dihydrothebaine, and shown to be different from the compound prepared in the latter way by Small and Browning (*J. Org. Chem.*, 1939, **3**, 618). Phenolic dihydrothebaine has been degraded to a nitrogen-free substance. Wolf–Kishner reduction of thebenone and β-thebenone yields isomeric phenols. The reduction of thebaine is concentrated hydrochloric acid with zinc affords a bimolecular substance of unknown constitution.

The reduction of organic compounds by sodium dissolving in liquid ammonia, with or without an additional proton source such as alcohol, has been shown to follow in many cases a course similar to that of the reduction with sodium and alcohol (Birch, *J.*, 1945, 809; *Nature*, 1946, **158**, 585). As the reduction of thebaine (I) by the latter process results in reductive scission of the allylic ether group and production of "phenolic dihydrothebaine" * (Freund and Holtoff, *Ber.*, 1899, **32**, 168; Small and Browning, *J. Org. Chem.*, 1939, **3**, 618), the reduction of thebaine under the conditions of the sodium–liquid ammonia method was investigated. The reduction (Bentley and Robinson, *Experientia*, 1950, **6**, 353) proceeded very rapidly in the absence of alcohol to give dihydrothebaine-ϕ in yields of up to 90%, thus providing a much more convenient method of preparing the base than that available hitherto. Dihydrothebaine-ϕ has been formulated as (II) (Small and Browning, *loc. cit.*) and we adopted this view until it was found to be inconsistent with the failure of attempts to convert the base into derivatives of 14-bromothebainone (III) by methods analogous to those used for the preparation of 14-bromocodeinone (IV) from thebaine (Freund, *Ber.*, 1906, **39**, 844) and of attempts to add benzoquinone or maleic anhydride to the base, its methiodide, and methyl ether methiodide. Stork (*J. Amer. Chem. Soc.*, 1951, **73**, 504) has shown from a study of the ultra-violet and infra-red absorption spectra



(I)



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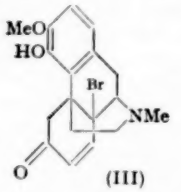

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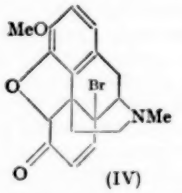


(IV)

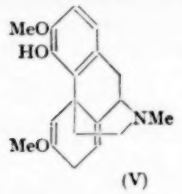
of thebaine, β-dihydrothebaine (Schmid and Karrer, *Helv. Chim. Acta*, 1950, **33**, 863), and dihydrothebaine-ϕ that (II) is in fact the structure of β-dihydrothebaine, whilst dihydrothebaine-ϕ is to be represented by the only other feasible formula, (V), and must arise in the sodium–liquid ammonia reduction by 1 : 4-addition of electrons to the allylic ether system.

Contrary to the statement of Freund and Holtoff (*loc. cit.*) dihydrothebaine-ϕ methiodide is readily degraded by hot alkali to a methine base, shown by ultra-violet and infra-red spectral measurements to be (VI) (Fig. 2), the 5 : 6-double bond having moved into conjugation under the influence of the hot alkali in a manner analogous to the well-known

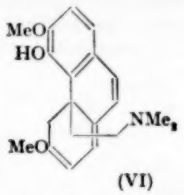
* The term "phenolic dihydrothebaine" accords with no recognised system of nomenclature and is especially cumbrous in the case of derivatives. We suggest the use of the expression dihydrothebaine-ϕ (not ϕ-dihydrothebaine, which could be confused with phenyldihydrothebaine).

Secondly, we propose to adopt the name "codeimethine" instead of the familiar "methylmorphimethine." This alternative appears simple and logical. It also avoids ambiguity in the case of certain derivatives.

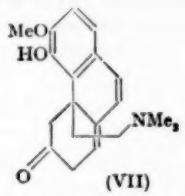
isomerisation of α-codeimethine (VIII) to β-codeimethine (IX) (Gulland and Robinson, *Mem. Proc. Manchester Lit. Phil. Soc.*, 1925, **69**, 79). The base (VI) should thus be termed



(V)



(VI)

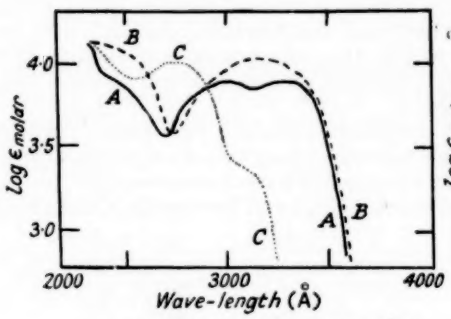


(VII)

β-dihydrothebaine methine, though its production by the Hofmann degradation of β-dihydrothebaine has not yet been attempted owing to the inaccessibility of the base. Hydrogenation of (VI) proceeded rapidly with absorption of two molecules of hydrogen, to give, probably, a mixture of stereoisomers since no crystalline derivatives could be obtained.

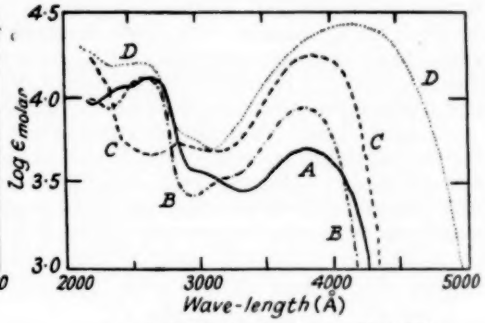
Hydrolysis of (VI) with mineral acid gave thebainone-B methine (VII), the ultra-violet absorption spectrum of which closely resembles that of β-codeimethine * (IX)

FIG. 1.



——— *A, Thebainone-B methine* (VII).
— — — *B, β-Codeimethine* (IX).
. . . . . *C, α-Codeimethine* (VIII).

FIG. 2.



——— *A, β-Dihydrothebaine methine* (VI).
— . — . — *B, 6-Methoxythebentriene.*
— — — — *C, Product of reduction of thebaine with zinc and concentrated hydrochloric acid.*
. . . . . *D, Piperonylidenethebainone B methine.*

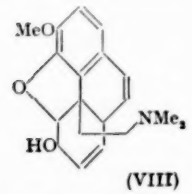
whilst that of α-codeimethine (VIII) in which only one double bond is conjugated with the aromatic nucleus is markedly dissimilar (Fig. 1). The piperonylidene derivative of (VII) shows an intense absorption band in the region 3000—5000 Å, indicative of the presence of a highly conjugated system (Fig. 2).

These results are sufficient to eliminate the isomeric αβ-unsaturated ketone structure for thebainone-B methine. Hydrolysis of dihydrothebaine-φ methiodide with hot sulphurous acid was reported by Freund and Holtoff (*loc. cit.*) to give "*iso*dihydrothebaine" (m. p. 138°; hydriodide, 235°; methiodide, 205°) whereas we find that the reaction affords thebainone-B methine (m. p. 184°; hydriodide, 215°; methiodide, 210°) in good yield. The same reaction occurs under the influence of warm mineral acid. Dihydrothebaine-φ methyl ether methiodide has also been degraded to a methine base (Freund and Holtoff, *loc. cit.*), which on hydrolysis affords thebainone-B methyl ether methine.

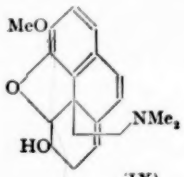
The nitrogen-containing ring of dihydrothebaine-φ, which shows a tendency to break on treatment with sulphurous acid, to give thebainone-C (X) (Bentley and Wain, following

* The ultra-violet absorption of α-codeimethine was at one time thought to be inconsistent with a styrenoid constitution (cf. Robinson, Anniversary Address Roy. Soc., 1947) but a further examination of models such as eugenol and *iso*eugenol, and their derivatives, has removed this obstacle. The spectra remain somewhat anomalous and fuller elucidation of the subject is needed.

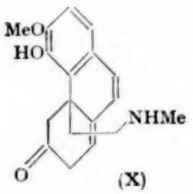
communication), is apparently so further weakened by conversion into the methiodide that fission of the ring can occur very readily. Thebainone-B methiodide undergoes degradation to (VII) in the same way, and a preliminary experiment indicates that β-dihydrothebaine methiodide also suffers degradation by acids to the salt of a sensitive base. The intermediate in all these reactions is doubtless thebainone-B methiodide,



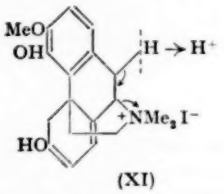
(VIII)



(IX)



(X)

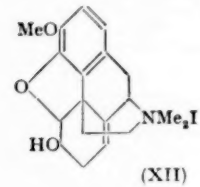


(XI)

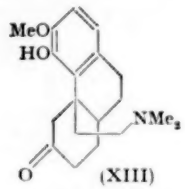
which in its enolic form (XI) allows the formation of a conjugated system by fission of the nitrogen ring with the introduction of a 9 : 10-double bond. Neopine methiodide (XII), which cannot develop a similar conjugated system, is unaffected by hot acids. It is noteworthy that thebaine methiodide does not undergo a similar degradation, but this is possibly related to the ease with which thebaine undergoes other rearrangements in acid solution.

Hydrogenation of thebainone-B methine resulted in production of β-dihydrothebainone dihydromethine (XIII), further characterised by conversion into β-thebenone (XIV), these products being identical with those obtained by Small and Browning (*loc. cit.*) from β-thebainone, hydrogen addition at $C_{(14)}$ occurring in the configuration abnormal in the morphine series. Hofmann degradation of (VII) involved the loss of a volatile base, but the nitrogen-free substance could not be isolated.

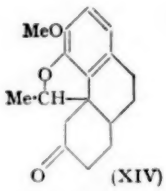
It may be noted here that production of a compound allotted the structure (VII) by the degradation of 14-hydroxydihydrothebainone methine (XV) was reported by Schöpf and and Borkowsky (*Annalen*, 1927, **452**, 248), but, whereas (VII) has been shown to give β-dihydrothebainone dihydromethine on hydrogenation, Schöpf and Borkowsky's base gave a different substance that was not analysed.



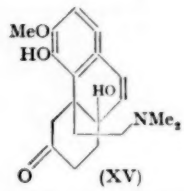
(XII)



(XIII)



(XIV)



(XV)

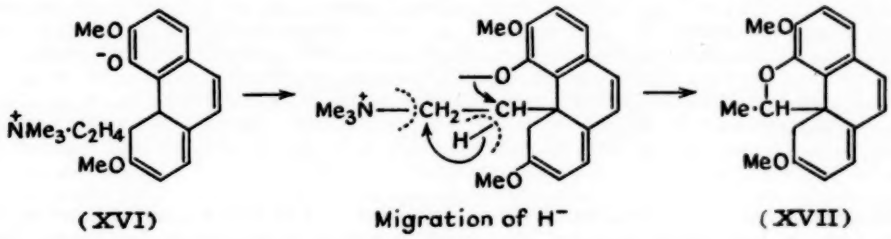
β-Dihydrothebaine methine (VI) undergoes further Hofmann degradation with loss of trimethylamine and production of 6-methoxythebentriene (XVII) which retains the residue of the nitrogen-containing ring as part of a cyclic ether of thebenone type. Apparently production of this cyclic ether system stabilises the product as when this is impossible, in the methyl ether of (VI), loss of the side chain occurs and 3 : 4 : 6-trimethoxyphenanthrene is obtained (Freund, *Ber.*, 1905, **38**, 3234). It is reasonable therefore to assume that during the degradation of (VI) a vinyl group does not appear as such at $C_{(13)}$, as this would result in immediate loss of ethylene as in the methyl ether series, there being no plausible mechanism by which a vinyl group could cyclise with the phenolic hydroxyl group in alkaline solution. The ease of loss of trimethylamine in degradations resulting in thebenone ring closure suggests that the same mechanism is operative in all cases. This mechanism is very probably (XVI) ⟶ (XVII) as illustrated.

In a similar manner (XVIII) degrades as shown to (XIX) (Robinson, unpublished work).

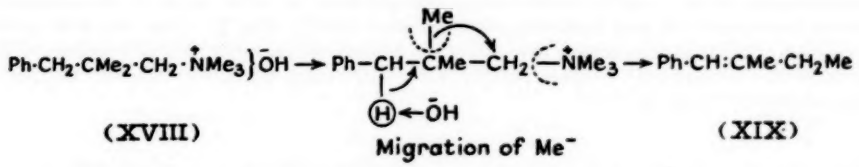
Hydrolysis of 6-methoxythebentriene yielded theben-8(14) : 9-dien-6-one (XX) which is very sparingly soluble in all solvents and has not been subjected to reduction.

When the $C_{(14)}$-epimeric ketones thebenone and β-thebenone (XIV) were reduced

under the drastic conditions of Huang-Minlon's modification of the Wolf–Kishner method (Huang-Minlon, *J. Amer. Chem. Soc.*, 1946, **68**, 2487) demethylation accompanied reduction, the products being morphoran and β-morphoran (XXI) respectively, though in one reduction of thebenone a small amount of the methyl ether of morphoran was obtained.

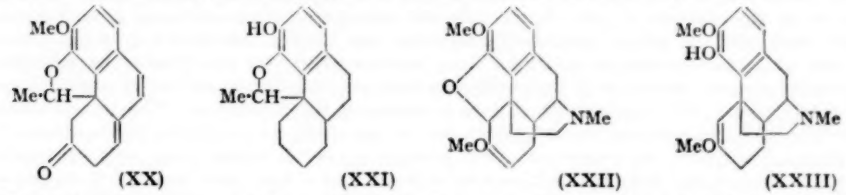


(XVI) Migration of H⁻ (XVII)



(XVIII) Migration of Me⁻ (XIX)

Attempts to oxidise dihydrothebaine-φ to a bimolecular derivative by silver nitrate (Goto, *J. Chem. Soc. Japan*, 1929, **50**, 603) led to a mixture, but as nitric acid is produced during this oxidation hydrolysis in part to thebainone derivatives may well occur.



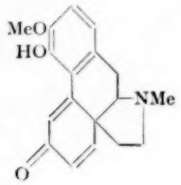
(XX) (XXI) (XXII) (XXIII)

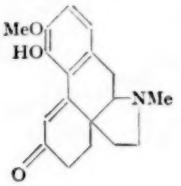
Following the success of the sodium–liquid ammonia reduction of thebaine, dihydrothebaine (XXII) was reduced in the same way to obtain dihydrothebainone Δ^{5}-enol methyl ether (XXIII). [Stork (*loc. cit.*) points out that the allocation of structures to the Δ^{5}- and Δ^{6}-enol methyl ethers of dihydrothebainone by Small and Browning (*loc. cit.*) must be reversed, as these were based on a misconception of the structure of dihydrothebaine-φ. The revised nomenclature is used throughout this account.] From this reduction a hard granular crystalline solid, m. p. 145—146°, $[\alpha]_D^{17}$ −61·5° (in alcohol), was obtained, whereas Small and Browning report this enol ether, obtained by the catalytic reduction of dihydrothebaine-φ, as plates, m. p. 127—128°, $[\alpha]_D^{27}$ −8·0° (in alcohol). A repetition of the catalytic reduction of dihydrothebaine-φ over palladised strontium carbonate as catalyst (Small and Browning used platinum oxide) resulted in the same compound, m. p. 145—146°, as granular crystals, though these were mixed with a certain amount of gummy impurity, possibly the $C_{(14)}$-epimer of (XXIII). The compound from both sources gave dihydrothebainone in 95% yield on hydrolysis.

We regard this product, obtained in two independent ways, as the genuine dihydrothebainone Δ^{5}-enol methyl ether, and presume that Small and Browning's substance of lower melting point and rotation is a mixture, possibly with dihydrothebaine-φ, $[\alpha]_D^{18}$ +31·4°, though they report a very good yield of dihydrothebainone on hydrolysis of their compound. Dihydrothebainone Δ^{5}-enol methyl ether is presumably the intermediate in the reported reduction of dihydrothebaine to dihydrothebainone by sodium and amyl alcohol (Freund, Speyer, and Guttmann, *Ber.*, 1920, **53**, 2250), the enol ether being hydrolysed to the ketone during isolation of the product.

When thebaine is dissolved in concentrated hydrochloric acid a deep red-orange solution is obtained. This is believed to contain (XXIV) (Robinson, *Nature*, 1947, **160**, 815) which on reduction catalytically (Cahn, *J.*, 1933, 1038) or with stannous chloride (Pschorr, Pfaff, and Herrschmann, *Ber.*, 1905, **38**, 3160; Schöpf and Borkowsky, *Annalen*, 1927,

(XXIV)





(XXV)

458, 148) yields metathebainone (XXV). Reduction of this halochromic solution with zinc has now been shown to give a bimolecular derivative containing no keto-group, the ultra-violet spectrum of which shows strong absorption in the same region as for β-dihydrothebaine methine (VII) and 6-methoxythebentriene (XVII) (Fig. 2), from which it is concluded that the aromatic nuclei are probably joined through two double bonds. The substance is phenolic and couples readily with diazonium salts, but nothing further is known about its constitution.

Experimental.

Dihydrothebaine-φ (V).—Thebaine (110 g.) was suspended in liquid ammonia (1100 ml.) in a 1600-ml. Dewar flask, and clean sodium (17·6 g.) added in thin slices with mechanical stirring, the transitory orange colour first noted being finally replaced by a permanent deep blue colour (35 minutes). The solution was stirred for a further 10 minutes, the excess of sodium removed by the addition of a few drops of alcohol, and the solution cautiously poured into cold water (1000 ml.). A small amount of precipitate was formed but dissolved immediately on addition of sodium hydroxide solution. The phenolic base was precipitated by addition of either solid carbon dioxide or 2N-hydrochloridic acid, the solution remaining strongly ammoniacal throughout. The former method gave a somewhat purer product. The base was taken up in ether (5 l.), the extract washed well to remove ammonia, and the ether partly removed by distillation, whereupon the base separated as a white or very pale pink solid; this was collected when the extract had been concentrated to 400—500 ml. The yield was 87 g. of material sufficiently pure for most purposes. A further 12 g. of less pure material could be recovered from the ethereal solution. The remainder of the product was a red tar.

On recrystallisation from ethyl acetate–light petroleum (b. p. 80—100°) dihydrothebaine-φ was obtained as colourless prisms, m. p. 154° alone or mixed with a specimen prepared by sodium–alcohol reduction of thebaine (Small and Browning, *loc. cit.*). It had $[\alpha]_D^{18}$ + 31·4° (Found: C, 73·2; H, 7·3; N, 4·3; OMe, 17·5. Calc. for $C_{19}H_{23}O_3N$: C, 72·9; H, 7·3; N, 4·5; OMe, 19·8%). The *picrate* was obtained as rosettes of slender yellow needles, m. p. 176° (decomp.), on recrystallisation from alcohol containing 10% of benzene (Found: C, 55·4; H, 4·8; N, 10·3. $C_{25}H_{26}O_{10}N_4$ requires C, 55·4; H, 4·8; N, 10·3%).

O-*Acetyldihydrothebaine-φ*.—Dihydrothebaine-φ gave a black tar on treatment with acetyl chloride or acetic anhydride in pyridine, but the O-*acetyl* derivative was obtained by passing a stream of keten through a solution of the base (10 g.) in dry ether (800 ml.) for 6 hours, during which the solution became milky and a small quantity of brown tar separated. This tar dissolved when the mixture was shaken with water. The ethereal layer was separated, shaken with dilute potassium hydroxide solution (6 × 150 ml.), washed with water, dried (Na_2SO_4), and evaporated. The crystalline residue was recrystallised from light petroleum (b. p. 80—100°) (charcoal), giving O-*acetyldihydrothebaine-φ* as rosettes of slender, colourless prisms, m. p. 139° (3·5 g.) (Found: C, 71·3; H, 6·8. $C_{21}H_{25}O_4N$ requires C, 71·0; H, 7·0%).

The *picrate* was obtained as minute, canary-yellow prisms, m. p. 180° (decomp.), on crystallisation from 2-ethoxyethanol (Found: C, 55·1; H, 4·8; N, 9·9. $C_{27}H_{28}O_{11}N_4$ requires C, 55·5; H, 4·8; N, 9·6%).

Bromination of dihydrothebaine-φ or its acetyl derivative in glacial acetic acid in the presence of potassium acetate with one, two, or three molecular equivalents of bromine yielded intractable products.

Condensation of Thebaine Methiodide with Benzoquinone.—A solution of resublimed benzoquinone (0·3 g.) in chloroform (5 ml.) was added to a solution of thebaine methiodide (1 g.; m. p. 224°) in chloroform (5 ml.), a red colour immediately developing. The mixture was heated to boiling on the steam-bath and rubbed with a glass rod, whereupon a bright orange precipitate separated. This was collected, washed with chloroform, and dried. *" Thebaine-quinone" methiodide* was thus obtained as orange needles, m. p. 205° (decomp.) (Found: C, 55·6; H, 5·0; I, 23·3. $C_{26}H_{28}O_5NI$ requires C, 55·6; H, 5·0; I, 22·7%). The *adduct* was decomposed completely on recrystallisation from *cyclo*hexanone, to give thebaine methiodide, m. p. 224° alone or mixed with an authentic specimen (Found: C, 52·0; H, 5·3; I, 27·1. Calc. for $C_{20}H_{24}O_3NI$: C, 53·0; N, 5·3; I, 28·0%). Dihydrothebaine-ϕ and its methiodide were rather rapidly oxidised when warmed with benzoquinone in chloroform, and the base was decomposed on being heated with maleic anhydride in boiling benzene. Dihydrothebaine-ϕ methyl ether methiodide (Freund, *Ber.*, 1905, **38**, 3255), though not so rapidly oxidised, slowly darkened on being heated with benzoquinone. In no case could the production of any adduct be detected.

β-*Dihydrothebaine Methine* (VI).—Potassium hydroxide was added to a solution of recrystallised dihydrothebaine-ϕ methiodide (30 g.) in hot, air-free water, until oily drops formed in the resulting brown solution. The mixture was then refluxed for 30 minutes in an atmosphere of oxygen-free nitrogen. (Without this precaution the mixture rapidly became almost black and the product was extremely difficult to purify.) The mixture was then cooled in ice, and the liquid decanted from the brown glassy solid, which was washed twice with ice-cold water, and shaken with warm water (125 ml.) and ether (500 ml.). The solid dissolved in the ethereal layer, which was separated, washed with water (3 × 100 ml.), and dried (Na_2SO_4), and the ether was then evaporated. In this way β-*dihydrothebaine methine* was obtained as a brownish-yellow crystalline solid. It separated from light petroleum (b. p. 60—80°) as pale yellow, well-formed cubes, m. p. 99°, with a red-brown tint when viewed in thickness, or as small yellow prisms from methyl acetate (recovery not good) [Found: (From petroleum) C, 73·9; H, 8·0; N, 4·2. $C_{20}H_{25}O_3N$ requires C, 73·4; H, 7·7; N, 4·3. (From methyl acetate) C, 70·3; H, 7·7. $C_{20}H_{25}O_3N,0{\cdot}5CH_3{\cdot}CO_2CH_3$ requires C, 70·8; H, 7·7%]. It was readily soluble in all organic solvents except cold light petroleum. Its alcoholic solution gave an intense grey-violet colour with ferric chloride, and its alkaline solution an intense red colour with diazobenzenesulphonic acid. The methiodide, prepared in methanol, was very soluble in water and alcohols, but addition of aqueous sodium perchlorate to a solution of the salt in water precipitated the *methoperchlorate* which was obtained as apple-green, felted needles, m. p. 134°, on recrystallisation from 50% aqueous alcohol (Found: C, 56·8; H, 6·6; Cl, 8·2. $C_{21}H_{28}O_3N,ClO_4$ requires C, 57·1; H, 6·4; Cl, 8·0%).

β-*Dihydrothebaine methine picrate* was obtained as scarlet prisms, m. p. 159°, when alcoholic solutions of the base and picric acid were mixed in the correct proportions (Found: C, 55·8; H, 5·0; N, 10·0. $C_{26}H_{28}O_{10}N_4$ requires C, 56·1; H, 5·0; N, 10·1%). It decomposed on attempted recrystallisation from *iso*butanol. The picrate and the methoperchlorate appear to be stable but the free base decomposes, slowly in the dark, very rapidly in sunlight, to a black tar.

Reduction of β-*Dihydrothebaine Methine.*—β-Dihydrothebaine methine (3 g.) in alcohol (50 ml.) was shaken under hydrogen in presence of palladised strontium carbonate until absorption of hydrogen ceased (505 ml., 2 mols.). The solution was filtered from catalyst, during which process it assumed a deep violet colour which disappeared when the solution was evaporated. On distillation of the residue, the *tetrahydro*-derivative (a β-*hexahydrothebainemethine*) was obtained as a colourless oil, b. p. 200°/0·04 mm., $[\alpha]_D^{20}$ 0·0° (in alcohol) (Found: C, 72·3; H, 8·6. $C_{20}H_{29}O_3N$ requires C, 72·5; H, 8·8%). No crystalline derivatives could be obtained.

Thebainone-B Methine (VII).—(*a*) β-Dihydrothebaine methine (2 g.) was dissolved in 3N-hydrobromic acid (15 ml.) with warming, and, on cooling, a mass of colourless felted needles separated (2·2 g.). These were collected, washed with water, and recrystallised from water, giving *thebainone-B methine hydrobromide* as long colourless needles, m. p. 234° (decomp.) (Found: C, 58·1; H, 6·1; Br, 20·3. $C_{19}H_{23}O_3N,HBr$ requires C, 57·9; H, 6·1; Br, 20·3%). This gave an intense maroon colour with concentrated sulphuric acid, and its alcoholic solution gave a brown colour with ferric chloride, changing to a transient green on dilution with water. *Thebainone-B methine* was obtained as pale yellow needles on neutralisation of a warm solution of the hydrobromide with ammonia in presence of sodium dithionite (hydrosulphite). The solid was rapidly collected, washed, and dried *in vacuo*, during which processes it became violet. This colour became more intense during the recrystallisation from alcohol, which gave the methine as violet felted needles, m. p. 184°, stubbornly retaining solvent (Found: C, 72·0; H, 7·5; N, 4·1. $C_{19}H_{23}O_3N,0{\cdot}25EtOH$ requires C, 72·1; H, 7·5; N, 4·3%). The violet

colour of the alcoholic solution was discharged by the addition of one drop of aqueous sodium dithionite but rapidly returned in the air. The *hydriodide* was obtained as almost colourless prisms by dissolving the base in warm dilute hydriodic acid and cooling the mixture. On recrystallisation from hot water with the addition of sodium dithionite it was obtained as colourless prisms, m. p. 214° (Found: C, 51·7; H, 5·3. $C_{19}H_{23}O_3N$,HI requires C, 51·7; H, 5·4%). The *methiodide* prepared in benzene, crystallised from water as colourless needles, m. p. 210°, becoming blue on continued exposure to air (Found: C, 51·5; H, 5·8. $C_{20}H_{26}O_3NI$,0·5H_2O requires C, 51·7; H, 5·8%). The *piperonylidene* derivative was prepared by addition of sodium ethoxide to a hot alcoholic suspension of the hydriodide and piperonaldehyde, a blood-red solution being obtained. After 10 minutes this was diluted with four times its volume of water, and the precipitate was collected and recrystallised from alcohol, yielding dark brown-yellow plates, m. p. 192—193° (Found: C, 72·5; H, 6·2. $C_{27}H_{27}O_5N$ requires C, 72·5; H, 6·1%).

(*b*) Dihydrothebaine-ϕ methiodide (25 g.) was dissolved in boiling water (125 ml.), and sulphur dioxide passed through the solution for 15 minutes, during which the solution turned deep blue. The solution was boiled for a further 10 minutes to expel all sulphur dioxide, and allowed to cool, whereupon a mass of felted pale blue needles separated. These were collected, washed, and recrystallised from boiling water with the addition of sodium dithionite, affording thebainone-B methine hydriodide as colourless prisms, m. p. 214°. The m. p. of this salt, the hydrobromide (234°), and the free base (184°) were undepressed by addition of the corresponding derivatives prepared by the hydrolysis of β-dihydrothebaine methine.

Thebainone-B methine perchlorate was obtained as colourless prisms, m. p. 230° on recrystallisation from water, by addition of sodium perchlorate to a hot aqueous solution of the hydriodide (Found: C, 54·4; H, 5·8; Cl, 8·1. $C_{19}H_{23}O_3N$,$HClO_4$,0·5H_2O requires C, 54·1; H, 5·9; Cl, 8·4%).

(*c*) Dihydrothebaine-ϕ methiodide (1 g.) was dissolved in hot 5N-hydrochloric acid (10 ml.), and 10 drops of perchloric acid were added. On cooling, a mist of fine droplets appeared, but these rapidly solidified. The crystals were collected and recrystallised from water. They then had m. p. 230°, undepressed by the addition of thebainone-B methine perchlorate. The identity was further confirmed by comparison of their ultra-violet absorption spectra.

(*d*) Thebainone-B (Bentley and Wain, cf. following paper) was precipitated from an aqueous solution of the hydrobromide (2 g.) in the presence of sodium dithionite, the base taken up in ether, and methyl iodide added to the mixture. A sensitive methiodide separated. The ether was decanted and the mixture warmed with 5N-hydrochloric acid. Potassium iodide was added to the mixture, and the solution cooled, whereupon dark crystals of thebainone-B methine hydriodide separated. These were collected and recrystallised from water in the presence of sodium dithionite (charcoal). Insufficient material was obtained for full purification; it had m. p. 211°, undepressed by admixture with thebainone-B methine hydriodide, m. p. 214°.

Hydrogenation of Thebainone-B Methine.—Thebainone-B methine (10 g.) was suspended in alcohol (150 ml.) and shaken under hydrogen at room temperature and pressure in presence of palladised strontium carbonate until absorption of hydrogen ceased (1500 ml., 1·9 mols.). The solution was filtered from catalyst, which was washed twice with hot alcohol, and the combined solutions were evaporated. On cooling, β-dihydrothebainone dihydromethine crystallised and was collected (8 g.). It was obtained as almost colourless needles, m. p. 179° (alone or mixed with an authentic specimen), on recrystallisation twice from alcohol.

β-*Thebenone.*—The above base was converted into β-thebenone by Small and Browning's method (*loc. cit.*), the latter substance being obtained as almost colourless rods, m. p. 188°, on recrystallisation from alcohol (reported m. p. 189—190°). *Piperonylidene-β-thebenone*, prepared by the action of sodium ethoxide on a solution of β-thebenone and piperonaldehyde in hot alcohol, crystallised on cooling, and was obtained as golden-yellow plates, m. p. 189°, on recrystallisation from 2-ethoxyethanol (Found: C, 73·7; H, 6·0. $C_{25}H_{24}O_5$ requires C, 74·1; H, 5·9%).

Thebenone, prepared from dihydrothebainone dihydromethine (Wieland and Kotake, *Annalen*, 1925, **444**, 69) and recrystallised from alcohol, was obtained as almost colourless prisms, m. p. 135° (reported m. p. 134—136°). Its 2 : 4-*dinitrophenylhydrazone* was obtained as minute, orange prisms, m. p. 225°, on crystallisation from dioxan (Found: N. 12·2. $C_{23}H_{24}O_8N_4$ requires N, 12·4%).

β-*Dihydrothebaine methyl ether methine* (Freund, *Ber.*, 1905, **38**, 3255) was prepared by the Hofmann degradation of dihydrothebaine-ϕ methyl ether methiodide, in an atmosphere of nitrogen, the product being obtained as a pale, amber-coloured gum, from which, contrary to

Freund's statement, no crystalline methiodide could be obtained. No other derivative could be obtained crystalline. The base decomposed spontaneously on storage, with evolution of readily detectable amounts of amine.

O-*Methylthebainone-B Methine.*—(*a*) Dihydrothebaine-ϕ methyl ether methiodide (0·6 g.) was dissolved in hot water (5 ml.), and four drops of 60% perchloric acid were added. On cooling and scratching with a glass rod, almost colourless crystals of O-*methylthebainone-B methine perchlorate* separated (0·3 g.). These were collected and recrystallised from water, with the addition of a few mg. of sodium dithionite. The salt was thus obtained as colourless prisms, m. p. 169° (Found: C, 55·8; H, 6·0; Cl, 8·3. $C_{20}H_{25}O_3N,HClO_4$ requires C, 56·1; H, 6·1; Cl, 8·3%). This was shown to be the perchlorate of a base which was liberated on neutralisation of a hot solution with ammonia. The base could not be purified owing to its ready oxidation.

(*b*) β-Dihydrothebaine methyl ether methine (0·2 g.) was hydrolysed in the same way as dihydrothebaine-ϕ methyl ether methiodide, and found to yield the same perchlorate, m. p. 170°, undepressed by admixture with the perchlorate obtained from the latter hydrolysis.

6-*Methoxythebenone-6* : 8(14) : 9-*triene* (XVII).—β-Dihydrothebaine methine (15 g.) was refluxed with methyl iodide (10 ml.) in alcohol (20 ml.), and the alcohol evaporated. The resulting oily methiodide was dissolved in water (100 ml.), potassium hydroxide added to the hot solution until a brown oil separated, and the solution boiled until evolution of trimethylamine ceased. When the mixture was cooled in ice, the brown oil set to a glass, from which the liquid was decanted. The glass was washed with water and shaken with ether until no more would dissolve. After being dried (Na_2SO_4), the ethereal solution was evaporated, leaving a brown oil that solidified on trituration with light petroleum (b. p. 60—80°). The solid was collected and recrystallised from the same solvent (charcoal), giving 6-*methoxythebenone-6* : 8(14) : 9-*triene* as canary-yellow prisms, m. p. 88°, darkening slightly on exposure to sunlight (5 g.) (Found: C, 76·0; H, 6·5. $C_{18}H_{18}O_3$ requires C, 76·5; H, 6·39%). It was insoluble in alkali, and the diazobenzenesulphonic acid and ferric choride tests were negative. No picrate could be obtained, showing that the substance is not the isomeric 4-ethoxy-3 : 6-dimethoxyphenanthrene.

Thebenone-8(14) : 9-*dienone*-6-*one* (XX).—Concentrated hydrochloric acid (1 ml.) was added to a solution of 6-methoxythebentriene (0·5 g.) in alcohol (10 ml.). During 30 minutes the solution deposited pale yellow crystals which were collected and well washed with alcohol and water (0·3 g.). On recrystallisation from a relatively large amount of dioxan (poor recovery), *thebenone*-8(14) : 9-*dienone*-6-*one* was obtained as colourless prisms, m. p. 248° (Found: C, 75·7; H, 6·0. $C_{17}H_{16}O_3$ requires C, 76·0; H, 6·0%).

Morphoran (XXI).—Thebenone (1·5 g.) and 90% hydrazine hydrate (3·4 ml.) were added to a solution of sodium (1·8 g.) in diethylene glycol (50 ml.), and the mixture refluxed for an hour. Water was then distilled off until the b. p. of the mixture rose to 200°, whereafter the solution was refluxed for 6 hours, then cooled, and poured into water. No precipitate was obtained, but on acidification an oil separated, which was taken up in ether. Evaporation of the extract left a viscous oil that crystallised slowly on trituration with aqueous ethanol. After recrystallisation from this solvent, *morphoran* was obtained as large, iridescent, irregular, colourless plates, m. p. 103° (Found: C, 78·7; H, 8·3; OMe, 0·0. $C_{16}H_{20}O_2$ requires C, 78·6; H, 8·2%). Morphoran is readily soluble in most organic solvents, its alcoholic solutions give a green colour with ferric chloride, and its alkaline solutions an intense red colour with diazobenzenesulphonic acid.

In one experiment in which the time of reflux was limited to 3 hours a small amount of an alkali-insoluble by-product was obtained. This appears to be morphoran methyl ether (thebenan) and was obtained as colourless prisms, m. p. 86° on recrystallisation from alcohol, $[\alpha]_D^{20}$ 0·0° (methanol) (Found: C, 77·8; H, 8·3; OMe, 9·0. Calc. for $C_{17}H_{22}O_2,0{\cdot}25H_2O$: C, 77·7; H, 8·5; OMe, 11·8%). Goto and Mitsui (*Bull. Chem. Soc. Japan*, 1931, **6**, 197) give the antipode of thebenan as crystallising with $\frac{1}{4}H_2O$ and having $[\alpha]_D^{17}$ −3·1°. The m. p. was not cited but their material was dried at 70°; Goto and Shishido (*ibid.*, 1935, **10**, 252) give the m. p. of (+)- and (−)-thebenan (anhydrous) as 48—54°; Cahn (*J.*, 1926, 2652) reports a compound of the same structure as an oil.

β-*Morphoran*, obtained in a similar way from β-thebenone, formed minute, almost colourless prisms, m. p. 148°, on crystallisation from 50% aqueous alcohol (Found: C, 78·3; H, 8·4%).

Oxidation of Dihydrothebaine-ϕ with Silver Nitrate.—Dihydrothebaine-ϕ (1 g.) in ethanol (10 ml.) was treated with excess of silver nitrate solution, and the mixture warmed on the water-bath for ½ hour and set aside overnight. The mixture was then filtered from the precipitated silver and poured into water, excess of ammonia was added, and the base was collected at the pump and dried. On crystallisation from toluene a light brown powder was obtained, decom-

posing slowly without melting on being heated above 200°. Two crystal types and an amorphous substance could be detected under the microscope. The analytical data were unsatisfactory.

Dihydrothebainone Δ^5*-Enol Methyl Ether* (XXIII).—(*a*) Dihydrothebaine (Small, Fitch, and Smith, *J. Amer. Chem. Soc.*, 1936, **58**, 1457) (5 g.) was reduced with sodium (0·5 g.) in liquid ammonia (200 ml.), the excess of sodium removed by the addition of solid ammonium chloride, and the mixture cautiously poured into water (100 ml.). A small amount of precipitate formed, but this dissolved on the addition of sodium hydroxide. The phenolic base was precipitated by solid carbon dioxide and extracted with ether. The ethereal extract on evaporation left a very pale pink oil, that crystallised at once on being rubbed with methyl acetate, to give colourless crystals, m. p. 143—145° (4·7 g.). The *methyl ether* was obtained as large, hard, granular, colourless crystals, m. p. 145—146° (after three recrystallisations from methyl acetate), $[\alpha]_D^{17}$ −61·5° (in alcohol) (Found: C, 72·5; H, 7·9. $C_{19}H_{25}O_3N$ requires C, 72·8; H, 7·8%). The substance gave an intense red colour on treatment with diazobenzenesulphonic acid in alkaline solution. The *methiodide*, prepared in alcohol, was obtained as elongated prisms, m. p. 153°, on crystallisation from alcohol (Found: C, 52·3; H, 6·5. $C_{19}H_{25}O_3N,CH_3I$ requires C, 52·5; H, 6·1%).

(*b*) Dihydrothebaine-ϕ (5 g.) in alcohol (120 ml.) was shaken under hydrogen in the presence of palladised strontium carbonate at the room temperature until absorption of hydrogen ceased (about 20 hours). The filtered solution was evaporated, leaving a pink gum that crystallised when rubbed with methyl acetate. Dihydrothebainone Δ^5-enol methyl ether was obtained as colourless, granular crystals, m. p. 145—146° [undepressed when mixed with a specimen of the base prepared as in (*a*)], on recrystallisation from methyl acetate. The yield by this process was only about 50%, but the residue recovered from the methyl acetate mother-liquors contained considerably more of the base, as was shown by hydrolysis of the residue to dihydrothebainone in good yield.

The methiodide prepared in this way had m. p. 153°, undepressed on admixture with a specimen of the methiodide prepared as in (*a*).

Hydrolysis. Dihydrothebainone Δ^5-enol methyl ether (1 g.) was dissolved in warm 2N-hydrochloric acid (5 ml.). Crystals slowly appeared, and these passed into solution on dilution of the mixture to 25 ml. After 15 minutes the solution was neutralised with ammonia, and the precipitate collected and recrystallised from aqueous alcohol. Dihydrothebainone was obtained, m. p. 146—150° alone or mixed with an authentic specimen, m. p. 148—151° (yield before recrystallisation, 0·91 g.).

Reduction of Thebaine with Zinc and Concentrated Hydrochloric Acid.—Zinc turnings were added in portions of 0·5 g. each to a stirred solution of thebaine (5 g.) in concentrated hydrochloric acid (60 ml.), the temperature being kept below 30°. The orange-red colour of the solution first darkened, then became orange, and finally yellow, and deposited a yellow precipitate. The reduction occupied about 45 minutes. The mixture was poured into water (700 ml.), made alkaline with ammonia, and submitted to continuous ether-extraction. In this way, a yellow amorphous solid (2·4 g.) was obtained; it was freely soluble in organic solvents except ether and light petroleum. After three recoveries from light petroleum (b. p. 60—80°) it was amorphous and had m. p. *ca.* 202°. On one occasion fine yellow needles were obtained from aqueous methyl alcohol, and these had m. p. 264° but the quantity was insufficient for analysis. The substance was phenolic as shown by its solubility in alkali and the red colour given by the alkaline solution on treatment with diazobenzenesulphonic acid. The infra-red spectrum indicates that there is no carbonyl group in the molecule, and the molecular-weight determination of the amorphous substance indicated that the substance is bimolecular (Found: *M*, 559). Its solution in concentrated sulphuric acid is deep purple.

We thank Dr. F. B. Strauss for observation of the ultra-violet absorption spectra, the Department of Scientific and Industrial Research for a grant (to K. W. B.), and the Ministry of Education for a grant (to A. E. W.).

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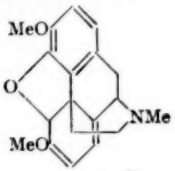
172. *The Morphine–Thebaine Group of Alkaloids. Part I. The Isomerism of the Thebainones.*

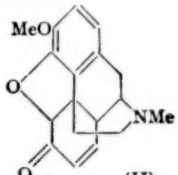
By K. W. Bentley and A. E. Wain.

A fourth thebainone has been prepared, by hydrolysis of dihydrothebaine-ϕ with acid. Structures have been allotted to all four isomers on the basis of infra-red and ultra-violet absorption data.

The reduction of thebaine (I) (Pschorr, Pfaff, and Herrschmann, *Ber.*, 1905, **38**, 3160; Schöpf and Borkowsky, *Annalen*, 1927, **458**, 148) and of codeinone (II) (Knorr, *Ber.*, 1905, **38**, 3171) with stannous chloride and concentrated hydrochloric acid, and catalytic hydrogenation of thebaine in >5N-hydrochloric acid (Cahn, *J.*, 1933, 1038) result in the production of a phenolic unsaturated ketone, originally called thebainone, but subsequently renamed metathebainone when it was realised that this base no longer contains the thebaine skeleton, having suffered migration of the side chain from $C_{(13)}$ to $C_{(14)}$, and is in fact (III) (Schöpf and Borkowsky, *loc. cit.*).



(I)



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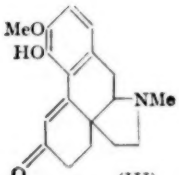

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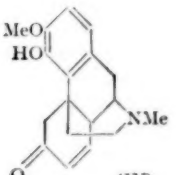
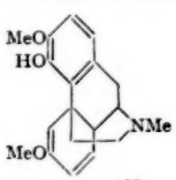


(IV)

Subsequently the true thebainone (IV) was isolated from the stannous chloride–hydrochloric acid reduction of thebaine and codeinone under slightly different conditions (Schöpf and Hirsch, *Annalen*, 1931, **489**, 224) and later (Small and Morris, *J. Amer. Chem. Soc.*, 1932, **54**, 2122; 1934, **56**, 2159) shown to be identical with the "sulphur-free ketone" obtained by the hydrolysis of β-ethylthiocodide (Pschorr, *Annalen*, 1910, **373**, 15). It has since also been prepared by hydrolysis of thebainone enol methyl ether (V) (Small and Browning, *J. Org. Chem.*, 1939, **3**, 618), and by the catalytic rearrangement of codeine (VI) (Weiss and Weiner, *J. Org. Chem.*, 1949, **14**, 194). Thebainone has been shown to have the structure (IV) by its smooth catalytic hydrogenation to dihydrothebainone (VII) (Schöpf and Hirsch, and Small and Browning, *loc. cit.*).



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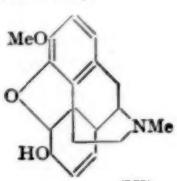

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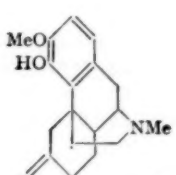
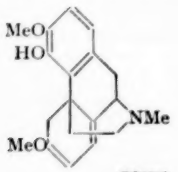


(VII)

Two other thebainones were isolated by Small and Browning from the products of hydrolysis of dihydrothebaine-ϕ [at that time believed to be (VIII), but now known to be (IX) (Stork, *J. Amer. Chem. Soc.*, 1951, **73**, 504)]. One of these (obtained by hydrolysis with potassium hydrogen sulphate) was believed to be the $C_{(14)}$ epimer of thebainone and was named β-thebainone, on the basis of its hydrogenation to β-dihydrothebainone and the degradation of the latter to a methine, dihydromethine, and nitrogen-free product (β-thebenone), during the whole course of which the isomerism between the two series persisted. β-Thebainone has since been obtained by hydrolysis of β-dihydrothebaine (Schmid and Karrer, *Helv. Chim. Acta*, 1950, **33**, 863) [first thought to be the $C_{(14)}$ epimer of (V), but now known to be (VIII) (Stork, *loc. cit.*)].

The other isomer of thebainone was obtained in very erratic and unsatisfactory yield by the hydrolysis of dihydrothebaine-ϕ with warm sulphurous acid, was named α-thebainone,

and was tentatively allotted the structure (X). Small and Browning further reported that hydrolysis of dihydrothebaine-ϕ with mineral acid gave only "coloured varnish-like substances," and suggested that under these conditions changes in addition to the simple hydrolysis of the enol ether group had occurred. By carrying out the hydrolysis with alcoholic hydrobromic acid we have isolated as hydrobromide a fourth thebainone, further



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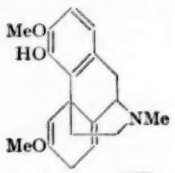
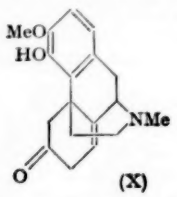
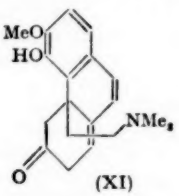


(IX)



(X)



(XI)

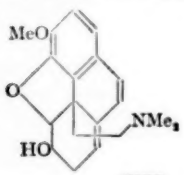
characterised as its picrate, and we have been able to show that the same substance is produced by hydrolysis of dihydrothebaine-ϕ with aqueous hydrochloric or perchloric acids. The free base rapidly degenerates to highly coloured substances. This thebainone was hydrogenated as the hydrobromide in aqueous solution, affording a 90% yield of dihydrothebainone.

It is clear that the existence of four isomeric thebainones can only be reasonably explained on the assumption that in one of them the nitrogen-containing ring has been broken with the introduction of a double bond between $C_{(9)}$ and $C_{(10)}$, and it seemed very probable that this has occurred during the production of Small and Browning's α-thebainone [compare the hydrolysis of dihydrothebaine-ϕ methiodide by hot sulphurous acid to the hydriodide of the base (XI), erroneously named α-thebainone methine (Bentley and Robinson, *Experientia*, 1950, **6**, 353)]. On the basis of this explanation two of the thebainones should be αβ-unsaturated and two βγ-unsaturated ketones. This question could not be settled by investigation of the ultra-violet absorption spectra of the thebainones as the ultra-violet absorption of the carbonyl group is masked in the morphine series by that of the aromatic nucleus, so attention was directed to the infra-red absorption of the four isomers. The following values were found for the carbonyl absorption frequencies in the infra-red:

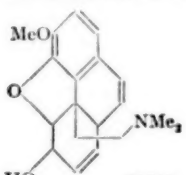
Thebainone perchlorate 1677 cm.$^{-1}$
β-Thebainone perchlorate 1671 cm.$^{-1}$
α-Thebainone perchlorate 1709 cm.$^{-1}$
New thebainone hydrobromide 1711 cm.$^{-1}$

These frequencies are slightly lower than normal, probably owing to hydrogen bonding in the solids, but they are clearly divided into two pairs, those of thebainone and β-thebainone being attributable to a carbonyl group conjugated with a double bond, whilst those of α-thebainone and the new thebainone are attributable to a normal non-conjugated carbonyl group.

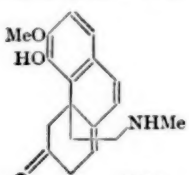
The absorption of the four compounds in the ultra-violet was next studied and found to allow a clear differentiation between α-thebainone and the other three isomers. The absorption curves of thebainone, β-thebainone, and the new thebainone are close to that of



(XII)



(XIII)



(XIV)

dihydrothebaine-ϕ (Fig. 1), the absorption in these cases being attributable to the guaiacol nucleus only; the spectrum of α-thebainone shows greatly increased absorption, and absorption at longer wave-lengths, as in the case of β-codeimethine (XII) and the base

(XI) in which two double bonds are conjugated with the aromatic nucleus, the absorption being greater than with α-codeimethine (XIII) in which only one double bond is conjugated with the nucleus (Fig. 2). These results leave no doubt that the new thebainone has the structure originally allotted by Small and Browning to α-thebainone, whilst the latter must now be allotted the structure (XIV).

The nomenclature of the thebainones is now seen to be in a state of confusion; for example, β-thebainone refers to a compound with one configuration at $C_{(14)}$, but α-thebainone does not refer to its epimer, and β-thebainone is a closer relative of thebainone than is the α-isomer. We propose, therefore, the re-naming of all four thebainones as indicated below: *

Old name	New name	Structure
Thebainone	Thebainone-A	(IV)
β-Thebainone	β-Thebainone-A	(IV) $C_{(14)}$-epimer
" New thebainone "	Thebainone-B	(X)
α-Thebainone	Thebainone-C	(XIV)

The name " α-thebainone methine " given to (XI) by Bentley and Robinson (*loc. cit.*) is now an obvious misnomer, as the nitrogen ring is already broken in " α-thebainone; " in fact (XI) is related to thebainone-B and its correct name is thebainone-B methine.

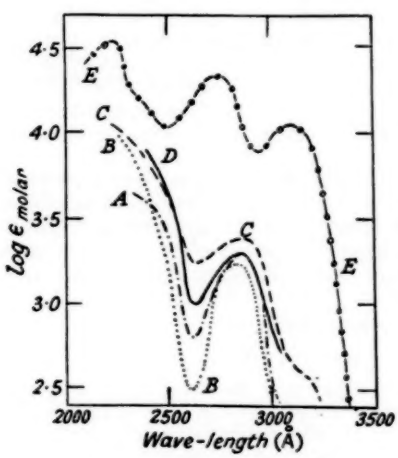


FIG. 1.

A, New thebainone obtained by hydrolysis of dihydrothebaine-φ with mineral acid.

B, Dihydrothebaine-φ.

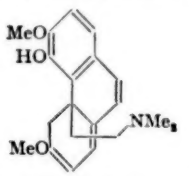
C, β-Thebainone.

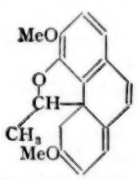
D, Thebainone.

E, α-Thebainone.

On the basis of structure (IX) for dihydrothebaine-φ it is clear that thebainone-B must be an intermediate in the hydrolysis of this base to β-thebainone-A with potassium hydrogen sulphate, and in fact it is gradually converted into the latter in an aqueous solution of potassium hydrogen sulphate. The hydrolysis of dihydrothebaine-φ to thebainone-C, however, must be an independent process, as no trace of this base (easily recognised by its

(XV)





(XVI)

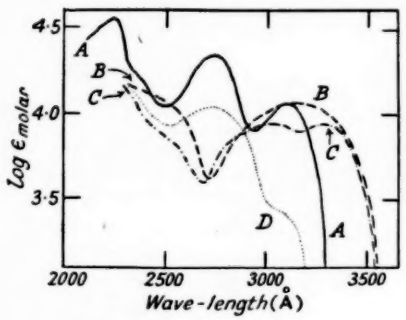
intense eosin-red colour with concentrated sulphuric acid, with which the other three isomers give only a pale straw colour) is formed when thebainone-B is kept in sulphur dioxide

* Where the position of the ethylenic linkings is now known with certainty, *e.g.*, in the thebainone and deoxycodeine series, ambiguity can be avoided by use of Δ to specify these positions. For instance, thebainone-A (IV) may be called Δ^7-thebainone, dihydrothebaine-φ (IX) may be called $\Delta^{5:8}$-dihydrothebaine, and dihydrothebainone Δ^5-enol methyl ether [(XXIII) of the preceding paper] may be called Δ^5-tetrahydrothebaine.—ED.

solution for several weeks. Tentative experiments indicate that thebainone-B methiodide is degraded to the hydriodide of (XI) by hot sulphurous acid in the same way as is dihydrothebaine-ϕ methiodide.

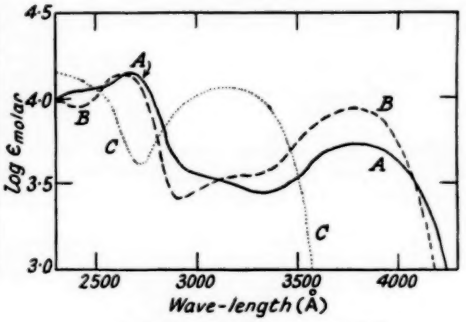
Although Stork (*loc. cit.*) has shown that dihydrothebaine-ϕ is to be represented by the structure (IX) and not by (VIII) (a formulation in agreement with our observation of its failure to undergo Diels–Alder addition of benzoquinone or maleic anhydride), there is no doubt on the basis of the ultra-violet absorption spectra (Fig. 3) that the methine base

FIG. 2.



A, α-*Thebainone*. *C*, (XI).
B, β-*Codeimethine*. *D*, α-*Codeimethine*.

FIG. 3.



A, (XV). *B*, (XVI). *C*, (XII).

obtained by the degradation of its methiodide and the nitrogen-free product (6-methoxythebentriene) have the structures (XV) and (XVI) allotted to them by Bentley and Robinson (*loc. cit.*), which were based as much on these spectra as on their methods of preparation. Doubtless the 5 : 6-double bond moves into conjugation with those at positions 8 : 14 and 9 : 10 under the influence of the hot alkali during the Hofmann degradation.

EXPERIMENTAL

(M. p.s. are uncorrected.)

Thebainone-B (X).—Dihydrothebaine-ϕ (5 g.) was dissolved in hot ethanol (20 ml.), the solution was cooled to 30°, and 48% hydrobromic acid (3 ml.) was added. After 10 minutes the solution deposited a large quantity of minute prisms when scratched. The solid (5 g.) was collected, washed well with cold alcohol and finally with ether, and stored in a vacuum-desiccator. The hydrobromide is apparently indefinitely stable when dry, but rapidly degenerates to a tar if left wet with alcohol. *Thebainone-B hydrobromide*, m. p. 205—207°, is sparingly soluble in organic solvents but very soluble in water and has $[\alpha]_D^{20}$ +15·84° (in water) (Found: C, 56·7; H, 5·9; Br, 20·8. $C_{18}H_{21}O_4N$,HBr requires C, 56·8; H, 5·8; Br, 21·0%). The base was obtained, as a pale yellow gum that rapidly degenerated on attempted crystallisation, by precipitation from a solution of the hydrobromide by potassium hydrogen carbonate in presence of sodium dithionite (hydrosulphite) and extraction with ether. The *picrate*, obtained by adding a solution of sodium picrate to an aqueous solution of the hydrobromide, formed bright yellow prisms, m. p. 183°, on recrystallisation from 2-ethoxyethanol (Found: C, 54·3; H, 4·9; N, 10·2. $C_{24}H_{24}O_{10}N_4$ requires C, 54·5; H, 4·55; N, 10·6%). The same picrate was obtained by hydrolysis of dihydrothebaine-ϕ with aqueous hydrochloric acid, precipitation of the product as the sparingly soluble gummy perchlorate, dissolution of the latter in hot water, and addition of aqueous sodium picrate. No other crystalline salts have been prepared from thebainone-B.

Thebainone-A (IV).—This was prepared by Schöpf and Hirsch's method (*loc. cit.*) and purified through the *perchlorate*. This was obtained as colourless plates, m. p. 149—150° (on recrystallisation from water), $[\alpha]_D^{21}$ −28·2° (in 50% alcohol) (Found: C, 51·6, 52·1; H, 6·2, 6·1. $C_{18}H_{21}O_3N$,$HClO_4$,H_2O requires C, 52·7; H, 5·8%).

β-*Thebainone-A* (IV).—This was prepared by Small and Browning's method (*loc. cit.*) and purified through the perchlorate, which is apparently dimorphic, as we obtained it as colourless prisms, m. p. 122—124° (reported as colourless six-sided plates, m. p. 149—157°). The base

obtained from this low-melting form was recovered, on recrystallisation from aqueous acetone, as long colourless needles, m. p. 99—100°, $[\alpha]_D^{21}$ +112° (in acetone) [reported m. p. 98—99°, $[\alpha]_D^{27}$ +114° (in acetone)] (Found: C, 68·1; H, 7·3. Calc. for $C_{18}H_{21}O_3N,H_2O$: C, 68·1; H, 7·25%).

Thebainone-C (XIV).—This isomer was prepared as directed by Small and Browning for " α-thebainone," and, as reported, the preparation was very troublesome. In our hydrolysis a white crystalline solid separated when the solution was set aside. This was presumably the bisulphite addition compound of a mixture of thebainones-B and -C, as it readily dissolved when the solution was heated and could not then be recovered. This substance was collected and dissolved in hot water, the solution cooled, and the base isolated as recommended by Small and Browning; after recrystallisation from acetone, a portion was found to have m. p. 186—187° (reported for " α-thebainone " 185—186°). *Thebainone-C perchlorate* was prepared, by the addition of aqueous sodium perchlorate to a solution of the base in dilute hydrochloric acid, and was obtained as colourless leaflets, m. p. 200° (decomp.) on recrystallisation from water in presence of a very small quantity of sodium dithionite (Found: C, 54·6; H, 5·6. $C_{18}H_{21}O_3N,HClO_4$ requires C, 54·2; H, 5·5%).

Hydrogenation of Thebainone-B Hydrobromide.—Thebainone-B hydrobromide (3·8 g.) in water (100 ml.) was shaken under hydrogen in presence of palladised charcoal. Hydrogen absorption did not begin until the solution had been heated to 80°. (In a comparative experiment using neopine hydrobromide, in which the double bond occupies a similarly sheltered position, absorption only began at 75°.) When absorption of hydrogen ceased the solution was freed from catalyst by filtration and neutralised with potassium hydrogen carbonate solution, which when kept gave a crystalline precipitate of dihydrothebainone (2·7 g.), m. p. 148—150° (from aqueous ethanol), undepressed on admixture with an authentic specimen.

Isomerisation of Thebainone-B.—(*a*) Thebainone-B hydrobromide (1 g.) was kept overnight in a solution of potassium hydrogen sulphate (2 g.) in water (15 ml.), after which the base was isolated and converted into the perchlorate, which after four recrystallisations from water was obtained as colourless irregular prisms, m. p. 122—123°, or m. p. 121—123°, when mixed with a specimen of β-thebainone-A perchlorate.

(*b*) Thebainone-B hydrobromide (1 g.) was kept for 3 weeks with a saturated solution of sulphur dioxide at 15—25°, with occasional warming to 40°. A crystalline solid, probably the bisulphite addition commpound of thebainone-B, separated but dissolved on addition of water and warming to 35°. Addition of perchloric acid to this solution gave no precipitate, but warming to 100° and cooling precipitated an oily perchlorate. This gave only a pale straw colour on dissolution in concentrated sulphuric acid and is probably unchanged thebainone-B perchlorate. No crystalline perchlorate could be isolated from the reaction mixture.

Thanks are tendered to Mr. D. C. McKean for the measurement of the infra-red absorption spectra of the thebainones, which were done on the solid salts in suspension in " Nujol " using a rock-salt prism and a Perkin-Elmer spectrometer, model 12C; to Dr. F. B. Strauss for the measurement of the ultra-violet absorption spectra of the thebainones; and to the Ministry of Education for a grant to one of us (A. E. W.). We also thank Professor Sir Robert Robinson for his interest in this work.

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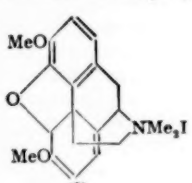
173. *The Morphine–Thebaine Group of Alkaloids. Part II.* The Reduction of Certain Quaternary Salts.*

By K. W. Bentley and A. E. Wain.

Sodium–liquid ammonia reduction of the methiodides of alkaloids of the morphine group has been shown to result in reductive scission of the nitrogen-containing ring, except in the case of dihydrothebainone Δ^5-enol methyl ether methiodide, which is reconverted into the parent base. In this way thebaine has been degraded to a nitrogen-free product.

Quaternary ammonium salts in the *iso*quinoline series have been reduced catalytically to dimethyl-2-*o*-tolylethylamines (Emde and Kull, *Arch. Pharm.*, 1936, **274**, 173) and degraded by sodium amalgam reduction to dimethyl-2-vinylbenzylamines (Emde, *Annalen*, 1912, **391**, 173), and Clayson (*J.*, 1949, 2016) has shown that sodium–liquid ammonia reduction of such quaternary salts follows the course of the catalytic reduction. As the morphine alkaloids are derivatives of *iso*quinoline the methiodides of some of these have been submitted to the sodium–liquid ammonia reduction, and in this way thebaine methiodide (I) has been shown to undergo reduction to dihydrothebaine-ϕ dihydromethine (II) in 70% yield; the same substance is obtained by similar reduction of dihydrothebaine-ϕ methiodide, and its methyl ether from dihydrothebaine-ϕ methyl ether methiodide. A further application of this reduction to the methiodide of (II) led to complete elimination of the nitrogen atom and production of 13-ethyl-7 : 8 : 9 : 13-tetrahydro-4-hydroxy-3 : 6-dimethoxyphenanthrene (III), a very unstable substance which spontaneously decomposed in a very short time. Hofmann degradation of the methiodide of (II) afforded 6-methoxytheben-5 : 8-diene (IV).



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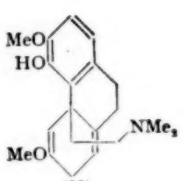

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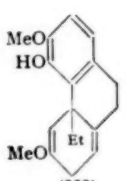

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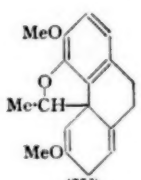


(IV)

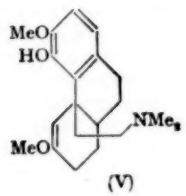
Catalytic reduction of dihydrothebaine-ϕ dihydromethine proved to be more difficult than that of dihydrothebaine-ϕ; as in the case of neopine and thebainone-B, in which the double bond occupies the same position as in (II) (Bentley and Wain, Part I of this series), reduction only occurred at a measurable rate at temperatures above 70°, under which conditions a base, presumably dihydrothebainone dihydromethine Δ^5-enol methyl ether (Δ^5-tetrahydrothebaine methine) (V), was obtained. The latter on hydrolysis yielded what appears to be the low-melting form of dihydrothebainone dihydromethine obtained by Cahn (*J.*, 1926, 2570) and Schöpf (Annalen, 1927, **452**, 266, footnote).

Hydrolysis of dihydrothebaine-ϕ dihydromethine with aqueous hydrochloric acid yielded thebainone-B dihydromethine (VI) (carbonyl absorption frequency in the infrared 1699 cm.$^{-1}$, compared with 1709 and 1711 cm.$^{-1}$ for the unconjugated carbonyl groups in thebainones-C and B, and 1677 and 1671 cm.$^{-1}$ for the conjugated carbonyl groups in thebainone-A and β-thebainone-A; Bentley and Wain, *loc. cit.*). Hofmann degradation of the methiodide of (VI) afforded with difficulty an oil which proved to be a mixture, probably of isomeric dehydrothebenones (VII) and (VIII), as the 8 : 14-double bond may well migrate in part into conjugation with the carbonyl group under the influence of the hot concentrated alkali. Dihydrothebaine-ϕ methyl ether dihydromethine proved to be an oil and was not further investigated.

Dihydrothebaine methiodide (IX) was next submitted to reduction with sodium in ammonia and found to give an intractable mixture of bases, not all of which were soluble in

* Part I, preceding paper.

alkali; the analytical data for the mixture indicated that it contained less hydrogen than corresponds to (V). When however dihydrothebainone Δ^5-enol methyl ether methiodide (Δ^5-tetrahydrothebaine methiodide) (X) (Bentley, Robinson, and Wain, *J.*, 1952, 958),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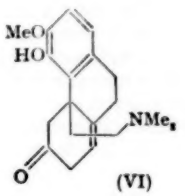
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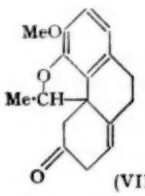
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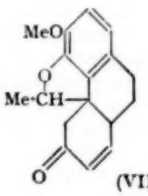
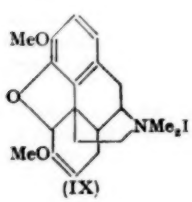

(VIII)

the expected intermediate in the sodium–ammonia reduction of dihydrothebaine methiodide, was reduced in this way only the undegraded parent base was recovered from the reaction in good yield. Presumably some reduction of the nitrogen-containing ring in dihydrothebaine methiodide occurs before scission of the cyclic ether, and dihydrothebaine dihydromethine (XI), which would be the product of such a reaction, is so sparingly soluble that no reduction takes place in liquid ammonia, as was verified by a separate experiment. This would account for the production of a non-phenolic substance during the reduction of dihydrothebaine methiodide. Neopine methiodide (XII) on reduction under these con-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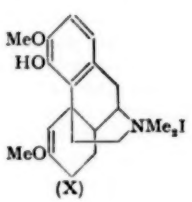
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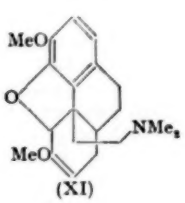
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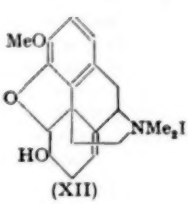
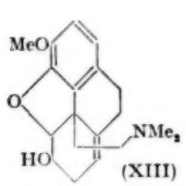

(XII)

ditions affords an excellent yield of neopine dihydromethine (XIII), identical with the product of sodium–alcohol reduction of α-codeimethine (XIV) (Vongerichten, *Ber.*, 1899, **32**, 1047; 1901, **34**, 2722) and the product of sodium amalgam reduction (Mosettig, *J. Org. Chem.*, 1940, **5**, 401) or mild catalytic reduction (von Braun and Cahn, *Annalen*, 1927, **451**, 55) of β-codeimethine (XV). The reduction of codeine methiodide appears to follow the same course, but other changes occur in addition, and this and similar reductions will be the subject of a later discussion.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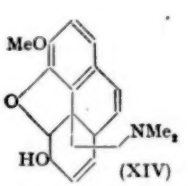
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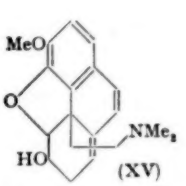
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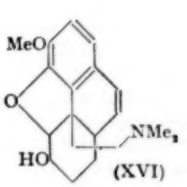
(XVI)

The reductive scission of the nitrogen-containing ring in the quaternary salts of the morphine alkaloids appears to proceed most smoothly when there is a double bond in the βγ-position relative to the nitrogen, *i.e.*, when the base is an allylamine (*e.g.*, thebaine, dihydrothebaine-ϕ, dihydrothebaine-ϕ methyl ether and neopine methiodides).

The methiodide of (XIII) is remarkably stable towards alkaline degradation, being unaffected by prolonged boiling in a concentrated potassium hydroxide solution, and only slowly suffering degradation by sodium *cyclo*hexyloxide in boiling *cyclo*hexanol (to give a mixture). This Hofmann degradation will be investigated more fully to determine whether any methylation of the alcoholic hydroxyl group occurs, as in the degradation of dihydrocodeine methine (XVI) (Rapoport, *J. Org. Chem.*, 1948, **13**, 714).

Experimental

(M. p.s are uncorrected.)

Dihydrothebaine-φ Dihydromethine.—(*a*) Sodium (17·2 g.) was added in thin slices to a mechanically stirred solution of thebaine methiodide (76 g.) in liquid ammonia (1500 ml.) during 1 hour, a permanent blue colour being finally obtained. During the reduction the solution first became pale green, a cream-coloured precipitate separated, and the colour then became deep red, changing through purple to the blue colour indicative of the presence of excess of sodium. The mixture was stirred for a further 5 minutes, the excess of sodium removed by the addition of solid ammonium chloride, and the solution cautiously poured into cold water (1·5 l.). A bulky flesh-coloured precipitate separated, but dissolved completely on addition of sodium hydroxide. Precipitation of the base was effected by the addition of 2N-hydrochloric acid, the solution remaining strongly alkaline with ammonia throughout. The base was taken up in ether (2 l.), and the ethereal solution washed twice with water, dried ($MgSO_4$), and evaporated, giving 50 g. of crude material. The base is very soluble in almost all solvents, the best for recrystallisation being ether, from which the recovery is only about 50%. Recrystallisation from ether yielded *dihydrothebaine-φ dihydromethine* (20 g.), m. p. 88—89°, $[\alpha]_D^{17}$ + 94·5° (in ethanol) (Found : C, 72·2, 72·3; H, 8·3, 8·3; N, 3·8; C-Me, 0·0. $C_{20}H_{27}O_3N$ requires, C, 72·8; H, 8·2; N, 4·2; C-Me, 0·0%).

A further 15 g. of the base was recovered by evaporating the mother-liquors to small bulk and cooling the residue in a freezing mixture; from the mother-liquors from this recovery 5·35 g. of thebainone-B dihydromethine were obtained on hydrolysis, making the total recoverable yield from thebaine 69%.

Dihydrothebaine-φ dihydromethine methiodide is readily soluble in water and in ethanol, but addition of sodium perchlorate to an aqueous solution precipitated the crystalline *methoperchlorate*, obtained as colourless needles, m. p. 253°, on recrystallisation from water (Found : C, 55·9; H, 6·5. $C_{20}H_{27}O_3N,CH_3ClO_4,\frac{1}{2}H_2O$ requires C, 55·8; H, 6·6%).

(*b*) Dihydrothebaine-φ methiodide (5 g.) was dissolved in liquid ammonia (150 ml.) in a Dewar flask, and sodium (0·91 g.) added, with mechanical stirring, in thin slices, a permanent blue colour being obtained. The mixture was stirred for a further 5 minutes, the excess of sodium removed by the addition of ammonium chloride, and the base isolated as above, in a yield of 2·81 g. of pure material, m. p. 88°, undepressed by the addition of a specimen of the base prepared by the reduction of thebaine methiodide.

Dihydrothebaine-φ Methyl Ether Dihydromethine.—Dihydrothebaine-φ methyl ether methiodide (5 g.) in liquid ammonia (200 ml.) was reduced as above with sodium (0·85 g.), the colour of the mixture changing through mauve and purple to deep blue. The base, isolated in the same way as dihydrothebaine-φ dihydromethine, proved to be a clear amber oil (3·6 g.), obtained as a pale amber glass on distillation, b. p. 63°/0·04 mm. (Found : C, 73·9; H, 8·5. $C_{21}H_{29}O_3N$ requires C, 73·5; H, 8·4%).

No crystalline derivatives could be obtained from this base, which has not been further investigated.

13-Ethyl-7 : 9 : 10 : 13-tetrahydro-4-hydroxy-3 : 6-dimethoxyphenanthrene.—Methyl iodide (5 g.) was added to a solution of dihydrothebaine-φ dihydromethine in alcohol (20 ml.), and the solution warmed on the water bath for 10 minutes, evaporated to 10 ml., poured into liquid ammonia (800 ml.), and treated with ethyl alcohol (10 ml.). Sodium (1·68 g.) was added in thin slices during 30 minutes to the stirred solution, traces of unchanged sodium were removed by ammonium chloride, and the mixture was poured cautiously into water (300 ml.). The phenol was precipitated by addition of 2N-hydrochloric acid, the solution remaining strongly alkaline with ammonia throughout. The precipitate was isolated by ether-extraction as a pale yellow oil, yielding a semi-opaque glass on distillation, b. p. 150—155°/0·05 mm. (Found : C, 75·2; H, 8·0. $C_{18}H_{22}O_3$ requires C, 75·5; H, 7·7%). The *phenol* was soluble in alkali, and the solution gave an immediate blood-red colour on the addition of diazobenzenesulphonic acid. Within 3 weeks the phenol had completely decomposed to a black tar.

6-Methoxytheben-5 : 8-diene (IV).—Dihydrothebaine-φ dihydromethine methiodide (from 1·1 g. of the base) was boiled with a solution of potassium hydroxide (15 g.) in air-free water (250 ml.) in a nitrogen atmosphere until evolution of amine ceased (about 3 hours), the mixture was cooled, and the liquid was decanted from the residual gum. The latter was shaken with ether and very dilute acetic acid, the ethereal layer separated, washed twice with water, then dried ($MgSO_4$), and the ether removed by distillation, leaving the *diene* as a light brown oil (0·76 g.). This was obtained as a pale yellow glass on distillation, b. p. 255—265° (bath-temp.)/8

mm. (Found: C, 76·2; H, 7·0. $C_{18}H_{20}O_3$ requires C, 76·1; H, 7·0%). The diazobenzenesulphonic acid reaction was negative.

Hydrogenation of Dihydrothebaine-φ Dihydromethine.—Dihydrothebaine-φ dihydromethine (2 g.) in alcohol (50 ml.) was shaken under hydrogen in the presence of palladised strontium carbonate. No absorption of hydrogen was noticed after 3½ hours at room temperature. Hydrogen absorption at a measurable rate began at 70°, and proceeded until one mol. of hydrogen had been absorbed. After filtration, the alcohol was removed by evaporation, leaving a clear very pale yellow glass (1·8 g.) which was obtained as a colourless glass on distillation, b. p. 185°/0·025 mm. (Found: C, 72·1; H, 8·[illegible]. $C_{20}H_{29}O_3N$ requires C, 72·5; H, 8·7%). This substance is presumably *dihydrothebainone dihydromethine* Δ^5*-enol methyl ether* (Δ^5*-tetrahydrothebaine dihydromethine*), as hydrolysis of a portion gave a base that on crystallisation from aqueous alcohol had m. p. 140°.

Thebainone-B Dihydromethine (VI).—Dihydrothebaine-φ dihydromethine (5 g.) was dissolved in warm N-hydrochloric acid (50 ml.), and the solution set aside for 10 minutes. On neutralisation with sodium carbonate in the presence of sodium dithionite (hydrosulphite) a flesh-coloured precipitate separated, and was collected at the pump, washed, and dried (3·6 g.). After three recrystallisations from aqueous alcohol, *thebainone-B dihydromethine* was obtained as almost colourless needles, m. p. 164° (Found: C, 72·0; H, 8·1. $C_{19}H_{25}O_3N$ requires C, 72·4; H, 7·9%). The *perchlorate*, prepared from the base and 60% perchloric acid in alcohol, was obtained as colourless prisms, m. p. 244—246°, on recrystallisation from water (Found: C, 54·6; H, 6·4; Cl, 7·8. $C_{19}H_{25}O_3N,HClO_4$ requires C, 54·9; H, 6·3; Cl, 8·5%). The *hydrobromide* was prepared in alcoholic solution and recrystallised from alcohol as colourless needles, m. p. 256—257° (Found: C, 57·6; H, 6·6; Br, 19·5. $C_{19}H_{25}O_3N,HBr$ requires C, 57·6; H, 6·6; Br, 20·0%). The *picrate* was precipitated from an aqueous solution of the hydrobromide by the addition of a solution of sodium picrate, and was obtained as clusters of bright yellow needles, m. p. 178—180°, on recrystallisation from alcohol (Found: C, 55·3; H, 5·2; N, 10·4. $C_{25}H_{28}O_{10}N_4$ requires C, 55·2; H, 5·1; N, 10·3%). The *methiodide*, prepared in alcohol, was obtained as colourless needles, m.p. 238°, on recrystallisation from 95% alcohol (Found: C, 51·6; H, 6·0; I, 27·2. $C_{19}H_{25}O_3N,CH_3I,\frac{1}{2}H_2O$ requires C, 51·5; H, 6·0; I, 27·3%). The *oxime* was obtained as colourless needles, m. p. 186—187°, on recrystallisation from 50% aqueous acetone (Found: C, 69·1; H, 8·2; N, 8·3. $C_{19}H_{26}O_3N_2$ requires C, 69·1; H, 7·9; N, 8·5%).

Hofmann Degradation of Thebainone-B Dihydromethine Methiodide.—Thebainone-B dihydromethine methiodide (1·4 g.) was boiled with 30% aqueous potassium hydroxide (30 ml.) until evolution of amine ceased (about 45 minutes), and the solution was cooled, acidified with hydrochloric acid, and extracted four times with chloroform (50 ml. portions). The extracts were washed with water, then dried, and the chloroform was removed, leaving a dark red oil, obtained as a yellow glass on distillation, b. p. 200—210° (bath-temp.)/0·075 mm. This substance was clearly a mixture, presumably of isomeric dehydrothebenones (the double bond having moved into conjugation with the carbonyl group in part under the influence of the hot alkali) as on storage for several weeks it was resolved into a crystalline solid and a dark yellow gum, both of which seem to be readily soluble in the same solvents, and have not yet been separated (Found, for mixture: C, 76·4; H, 6·8. Calc. for $C_{17}H_{18}O_3$: C, 75·5; H, 6·7%). The diazobenzenesulphonic acid reaction was negative for this compound, which was insoluble in aqueous alkali.

Reduction of Dihydrothebaine Methiodide.—Dihydrothebaine methiodide (18 g.) was reduced by sodium (2·85 g.) in liquid ammonia (400 ml.), and the product isolated as before. This proved to be an intractable mixture of bases, not all of which were soluble in alkali, one component apparently being crystalline, but it has not yet been possible to separate the mixture. No dihydrothebainone Δ^5-enol methyl ether could be isolated from the mixture (Found, for the mixture: C, 72·5; H, 8·3. $C_{20}H_{29}O_3N$ requires C, 72·5; H, 8·8. $C_{20}H_{27}O_3N$ requires C, 72·9; H, 8·2. Calc. for $C_{19}H_{25}O_3N$: C, 72·8; H, 7·8%).

Reduction of Dihydrothebainone Δ^5*-Enol Methyl Ether Methiodide.*—This salt (5·5 g.) was dissolved in liquid ammonia (200 ml.) and reduced with sodium (2·37 g.). The product, isolated in the usual way, was obtained as colourless granular prisms (2·7 g.), m. p. 144—146°, undepressed on addition of dihydrothebainone Δ^5-enol methyl ether.

Neopine Dihydromethine (XIII).—Neopine methiodide (10 g.) was reduced by sodium (1·15 g.) in liquid ammonia (300 ml.), the excess of sodium removed by the addition of a few drops of alcohol, and the solution poured cautiously into water (300 ml.). The resulting aqueous solution was saturated with ammonium chloride and extracted with ether (3 × 200 ml.), and the combined ethereal extracts were washed, dried, and evaporated, leaving a brown oil that was converted in part into the methiodide, pale yellow elongated prisms, m. p. 263° (from 90%

alcohol), $[\alpha]_D^{19}$ −31·3° (in water) (Found: C, 50·1; H, 6·0; I, 27·2. Calc. for $C_{19}H_{25}O_3N,MeI,H_2O$: C, 50·5; H, 6·3; I, 26·8%); the m. p. was not depressed by addition of the methiodide of neopine dihydromethine prepared by sodium–alcohol reduction of α-codeimethine. The *perchlorate*, prepared in alcohol, was obtained as colourless pointed prisms, m. p. 216—217°, $[\alpha]_D^{20}$ −27·7° (in 50% alcohol) on recrystallisation from 95% alcohol (Found: C, 55·3; H, 6·7; Cl, 8·5. $C_{19}H_{25}O_3N,HClO_4$ requires C, 54·9; H, 6·3; Cl, 8·5%).

Hofmann Degradation of Neopine Dihydromethine Methiodide.—This methiodide (0·5 g.) was boiled with 40% aqueous potassium hydroxide for 1 hour, during which no trace of amine was evolved, and on cooling the salt crystallised. 5 G. of the methiodide were accordingly boiled under reflux with a solution of 2 g. of sodium in 60 ml. of *cyclo*hexanol until evolution of amine ceased (about 3 hours), the *cyclo*hexanol was removed by steam-distillation, and the residue was extracted with ether, which on evaporation left a brown viscous oil from which no definite fraction could be isolated on distillation.

We thank Professor Sir Robert Robinson for his interest in this work, and the Ministry of Education for a grant to one of us (A. E. W.).

THE DYSON PERRINS LABORATORY, OXFORD UNIVERSITY. [*Received, October* 31*st*, 1951.]

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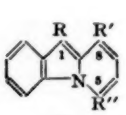
174. *Experiments on the Synthesis of the Ring Systems of Strychnine and Allied Alkaloids. Part II.**

By SIR ROBERT ROBINSON and J. E. SAXTON.

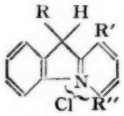
The " ethiodide " of 1 : 5 : 8-trimethyl-2 : 3-benzopyrrocoline (Robinson and Saxton, *J.*, 1950, 3136) is identical with the " methiodide " of 1-ethyl-5 : 8-dimethyl-2 : 3-benzopyrrocoline (*loc. cit.*) which proves that in the formation of these salts the β-carbon of the indole nucleus is ethylated, and methylated, respectively. It is apparent that these salts and also the hydracid salts of the benzopyrrocolines are pyridinium salts. Several new condensations of indole or its derivatives with 1 : 4-dicarbonyl compounds are described and in the case of a keto-aldehyde, namely lævulaldehyde (as its dimethyl acetal), it is found that the aldehyde group attacks position 1 (>NH). Thus with skatole the product is 1 : 8-dimethyl-2 : 3-benzopyrrocoline. An observation, which is of importance in further work in the direction of the strychnine skeleton, is that 2-methylfuran can replace the lævulaldehyde dimethyl acetal; a condensation with 3-ethylindole is mentioned as an example.

The condensation of indole with acetonylacetone has been re-examined; the products include 1 : 4-dimethylcarbazole.

IN our first paper on these topics (*J.*, 1950, 3136) we drew attention to the fact that the hydrochloride of 1 : 5 : 8-trimethyl-2 : 3-benzopyrrocoline (I; R = R′ = R″ = Me) must possess an entirely different constitution from the base, the substances not being in readily mobile equilibrium with each other in all usual circumstances. For example, ether does not extract the base from a dilute acid solution of the salt and the same acid (*e.g.*, 1% aqueous hydrochloric acid) does not extract the base from ethereal solution. Hence the base was considered to be markedly pseudomeric.



(I)



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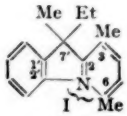


(III)

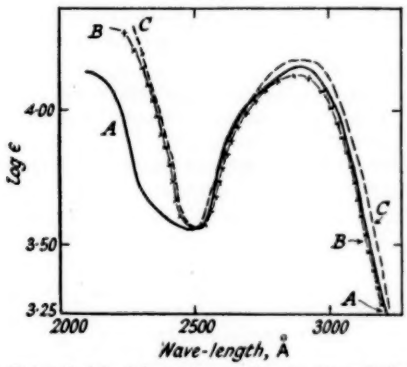
In the month which saw the publication of our communication an opportunity was taken to point out that the salt should be a pyridinium derivative of the structure (II)

* Part I, *J.*, 1950, 3136, has not hitherto been designated as such, but it is now seen to be the starting point of a series of investigations.

(R = R′ = R″ = Me) (Anniversary Address of the President of the Royal Society, November 30th, 1950; *Proc. Roy. Soc.*, *A*, **1951**, **205**, 1). The correctness of this suggestion has now been proved unequivocally.

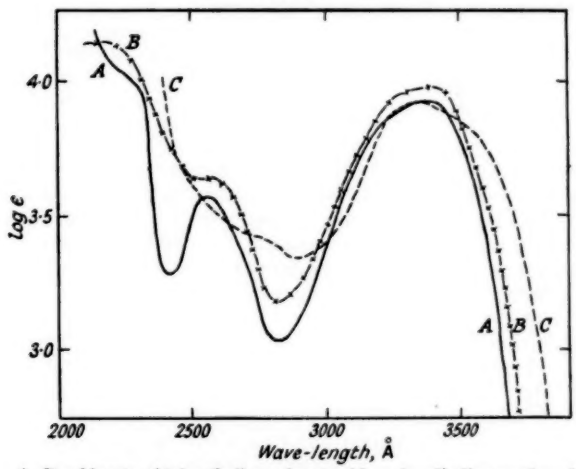
The benzopyrrocolines are feeble bases and react sluggishly with alkyl halides. Combination with methyl or ethyl iodide was effected in sealed tubes at 100°. It transpired, as was expected, that the " ethiodide " of 1 : 5 : 8-trimethyl-2 : 3-benzopyrrocoline was

FIG. 1.



A, 1 : 5 : 8-*Trimethyl*-2 : 3-*benzopyrrocoline in dilute hydrochloric acid.*
B, 1 : 5 : 8-*Trimethyl*-2 : 3-*benzopyrrocoline " methiodide " in water.*
C, 1 : 5 : 8-*Trimethyl*-2 : 3-*benzopyrrocoline " ethiodide " in water.*

FIG. 2.



A, Perchlorate of trimethylbenzylenepyridone in alkaline methanol.
B, Trimethylbenzylenepyridone in methanol.
C, Dehydrostrychninolone (*Prelog, Kocòr, and Taylor*, loc. cit.).

identical with the " methiodide " of 1-ethyl-5 : 8-dimethyl-2 : 3-benzopyrrocoline. This salt must therefore be (III), and the hydrochloride is (II) because of the close similarity of the ultra-violet absorption spectra (see Fig. 1). These spectra have no resemblance to those characteristic of the bases (*loc. cit.*) but, apart from a higher log ε, they are remarkably like those shown by 5 : 6 : 7 : 8-tetrahydro-1 : 5 : 8-trimethyl-2 : 3-benzopyrrocoline and by 9-ethyl-1 : 2 : 3 : 4-tetrahydrocarbazole. It is perhaps permissible to conclude from this correspondence that the constant factors are predominant and these are the unsaturation of the benzene ring and an unsaturated group in the five-membered ring fused with

it. Surprisingly it seems to be less important that to achieve this comparison we need to take –CMeEt–, –NEt–, and –NR– (where R is in ·CHMe·CH_2·CH_2·CHMe·) as the equivalent saturated groups of the said five-membered ring.

The formation of salts such as (III) is a typical *C*-alkylation of a hetero-enoid system (cf. Hamilton and Robinson, *J.*, 1916, **109**, 1029) and the products can only be termed "alkyl halides" if it is desired to indicate a relation to their generators.

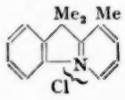
In this sense, (III) is both a "methiodide" and an "ethiodide," but in fact it is neither. We suggest that these substances should be named as pyridinium derivatives and the most important substituent is benzylene ·C_6H_4·CH_2· in which the side-chain carbon atom is numbered 7′ (for convenience of avoidance of α in the resulting nomenclature), and the *ortho*-carbon atom is numbered 2′.

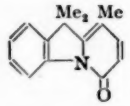
Inspection of the structure (III) shows that it includes certain characteristics of the strychnine molecule namely the ββ-disubstitution in the indole nucleus and three of the rings of the heptacyclic system of the alkaloid.

In order to make possible a nearer approach we desired to omit the substituent in the 5-position (cf. I). A methyl group in this position can be readily diagnosed by the formation of coloured salts on condensation with *p*-dimethylaminobenzaldehyde. One such dye has been analysed and is described in the Experimental portion.

On replacement of acetonylacetone in the condensation with skatole by lævulaldehyde dimethyl acetal, a dimethyl-2 : 3-benzopyrrocoline was produced. This must have the constitution (I; R = R′ = Me; R″ = H), rather than the alternative with H at 8 and Me at 5 because its "methiodide" did not exhibit the above-mentioned reaction with *p*-dimethylaminobenzaldehyde.

In an analogous synthesis with 3-ethylindole we found that the lævulaldehyde acetal could be replaced by 2-methylfuran, an observation which greatly enlarges the scope of our method. In the case of skatole itself, competing polymerisation renders the more reactive lævulaldehyde acetal the better starting point.

(IV) 



(V)

The constitution of 5 : 8-dimethyl-2 : 3-benzopyrrocoline was confirmed by oxidation of its "methochloride" (IV) to a pyridone (V); this could be effected by alkaline ferricyanide. This substance contains the chromophore of the so-called colourless benzylidene derivatives in the strychnine series (for example, that of *iso*dihydrostrychnine) to which one of us has frequently referred,* and more simply of dehydrostrychninolone (Prelog, Kocòr, and Taylor, *Helv. Chim. Acta*, 1949, **32**, 1052). The ultra-violet absorption spectrum of (V) (Fig. 2) is very like that of dehydrostrychninolone.

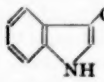
An interesting feature is that the spectrum in methanol is altered by the addition of sodium hydroxide. There is no hydroxyl group or other source of active hydrogen in the molecule and the only explanation of the result that we can envisage is based on electrostriction of the dipole or associated dipole by hydroxyl (or methoxyl) ions.

A related phenomenon is the formation of an abnormal perchlorate, $2B,HClO_4$. This we might formulate as $[H(-+)(-+)]^+ClO_4^-$. In that case both the dipoles included would be of pyridinium structure, or at least an intermediate form between neutral pyridone and full pyridinium dipole. An alternative hypothesis based on hydrogen bonding is expressed in the symbol $[(+-)H(-+)]^+ClO_4^-$.

The condensation of indole with acetonylacetone in ethanolic hydrogen chloride is now found to yield 1 : 4-dimethylcarbazole (Anderson and Campbell, *J.*, 1950, 2856), a new synthesis of which is described herein, and a substance, presumably $C_{14}H_{15}ON$, isolated

* Dr. A. M. Stephen (D. Phil. Thesis, Oxford Univ., 1949) and one of us found that the ultra-violet absorption of these substances resembled that of 1-phenyl-2-pyridone and accumulated other evidence of this type of structure. We were in correspondence with Professor V. Prelog who was cognisant of our work and very courteously acknowledged this in the communication of Prelog, Kocòr, and Taylor (*loc. cit.*).

as a semicarbazido-semicarbazone (VI). The latter forms a complex with two molecules of semicarbazide (cf. *J.*, 1950, 3137, 3139).



(VI)

Two further examples of the synthesis of carbazole derivatives from indole and 1 : 4-diketones are described in the Experimental section.

Experimental

Condensation of Indole with Acetonylacetone.—The mixture (1 g.) obtained from the interaction of indole and acetonylacetone under the conditions previously described (*J.*, 1950, 3139) was dissolved in aqueous ethanol (1 : 1), and excess of semicarbazide hydrochloride and sodium acetate in aqueous ethanol (1 : 1) added. The solution was gently heated for 5 minutes on the steam-bath and allowed to cool. The crystals that separated were collected, washed with water, ethanol, and ether, and dried at 100° *in vacuo*. This substance (0·4 g.), decomp. 242°, so obtained as dense, colourless rhombs, was insoluble in all ordinary organic solvents (Found : C, 43·5, 43·2; H, 6·5, 6·9; N, 36·9, 35·8. $C_{18}H_{32}O_4N_{12}$ requires C, 43·7; H, 6·7; N, 36·8%). These remarkable analytical results may be interpreted as follows. Condensation of 1 mol. of C_8H_7N with 1 mol. of $C_6H_{10}O_2$, with loss of $1H_2O$, gives $C_{14}H_{15}ON$, the semicarbazone of which is $C_{15}H_{18}ON_4$. The difference to be accounted for is $C_3H_{14}O_3N_8$, that is 3 mols. of semicarbazide. We are able (see below) to remove two molecules of semicarbazide and hence this substance is regarded as $C_{16}H_{23}O_2N_7,2CH_5ON_3$.

The complex (0·2 g.) was mixed with aqueous oxalic acid (10 c.c. of 30%) and heat applied until dissolution was complete. After cooling, the mixture was extracted with ether several times, and the combined extracts were washed with sodium carbonate solution and water, and evaporated. The residue separated from ethanol as colourless prisms, m. p. 240° (Found : C, 55·4; H, 7·0; N, 27·4. $C_{16}H_{23}O_2N_7$ requires C, 55·7; H, 6·8; N, 28·4%). This substance is thought to be the *semicarbazone* (VI) of 5-3′-indolyl-5-semicarbazidohexan-2-one.

The mother-liquors from the semicarbazone preparation described above were diluted with much water, and the product collected, and crystallised from aqueous ethanol. 1 : 4-Dimethylcarbazole (0·7 g.) was obtained as long, colourless needles, m. p. 97—98° (Found : C, 86·0; H, 6·7; N, 7·3. Calc. for $C_{14}H_{13}N$: C, 86·2; H, 6·7; N, 7·2%). Dr. N. Campbell kindly provided a specimen of his 1 : 4-dimethylcarbazole which had m. p. 82—86° (Anderson and Campbell, *loc. cit.*, m. p. 79—82°); on admixture with our specimen the m. p. was 82—91°. The picrate crystallised from ethanol or benzene as red needles, m. p. 151—152° (decomp.) (Anderson and Campbell, *loc. cit.*, give m. p. 142—143°) (Found : C, 56·7; H, 3·8; N, 13·2, 13·5. Calc. for $C_{14}H_{13}N,C_6H_3O_7N_3$: C, 56·6; H, 3·8; N, 13·2%).

Synthesis of 1 : 4-*Dimethylcarbazole.*—A mixture of *p*-xylylhydrazine (2 g.) and *cyclo*hexanone (1·5 g.) was heated on the steam-bath for a few minutes—until hydrazone formation appeared to be complete. In an earlier experiment the derivative was isolated and crystallised from ethanol in orange prisms, which when kept overnight in an evacuated desiccator decomposed to a brown tar. Hence the substance was not completely purified in this synthesis. The mixture was cooled and, when no further crystallisation occurred, the product was collected and washed with a little cold ethanol. This *cyclo*hexanone *p*-xylylhydrazone was added to 10% sulphuric acid (100 c.c.), and the mixture boiled for 30 minutes. The product was isolated by means of ether and crystallised from light petroleum (b. p. 40—60°). After one crystallisation 5 : 6 : 7 : 8-tetrahydro-1 : 4-dimethylcarbazole (1 g.) was obtained as colourless needles, m. p. 86—88°; Anderson and Campbell, *loc. cit.*, give m. p. 88—89°. A solution of the tetrahydrodimethylcarbazole (0·75 g.) and chloranil (2 g.) in the minimum volume of sulphur-free xylene was refluxed until a few drops of the liquid developed no red colour with hot aqueous sodium hydroxide (4 hours). The solution was cooled, separated from tetrachloroquinol, diluted with ether, shaken with sodium hydroxide solution, and dried. The solvents were removed, and the product was dissolved in light petroleum (b. p. 80—100°). Purification was effected by adsorption on an alumina column, the product being eluted with light petroleum (b. p. 60—80°)–benzene (3 : 1). 1 : 4-Dimethylcarbazole (0·25 g.) separated from light petroleum (b. p. 40—60°) as colourless needles or prisms, m. p. 96—97°, alone or when mixed with the specimen obtained from indole and acetonylacetone (Found : C, 86·3; H, 6·7; N, 7·3. Calc. for $C_{14}H_{13}N$: C, 86·2; H, 6·7; N, 7·2%). The picrate crystallised from ethanol as red needles,

m. p. 152° (decomp.), alone or mixed with the picrate of the product from indole and acetonylacetone.

The absorption of 1 : 4-dimethylcarbazole in the ultra-violet closely resembles that of carbazole as the following data show (values of $\log_{10} \varepsilon$ in parentheses). Carbazole: Maxima, 2350 (4·26), 2550 (4·20), 2930 (4·18), 3220 (3·53), 3350 (3·47); minima, 2500 (4·12), 2700 (3·52), 3080 (3·41), 3310 Å (3·40). 1 : 4-Dimethylcarbazole: Maxima, 2350 (4·30), 2600 (4·04), 2890 (4·15), 3220 (3·6), 3350 (3·6); minima, 2550 (3·95), 2740 (3·75), 3000 (3·21), 3310 Å (3·51).

7′-Ethyl-3 : 6 : 7′-*trimethyl*-1 : 2(2′ : 7′)-*benzylenepyridinium Iodide* (III).—A mixture of 1 : 5 : 8-trimethyl-2 : 3-benzopyrrocoline (1 g.) and ethyl iodide (5 c.c.) was heated at 100° for 3—4 hours in a sealed tube. The product was collected, washed with ether, and crystallised from water or ethanol. *7′-Ethyl*-3 : 6 : 7′-*trimethyl*-1 : 2(2′ : 7′)*benzylenepyridinium iodide* was obtained as colourless or very pale yellow prisms, m. p. 247—249° (decomp.) (Found: C, 56·2; H, 5·6; I, 35·3. $C_{17}H_{20}NI$ requires C, 55·9; H, 5·5; I, 34·8%). This quaternary salt furnished a deep red dye on being heated with *p*-dimethylaminobenzaldehyde or *p*-nitrosodimethylaniline in ethanol in the presence of a trace of piperidine (see below).

Interaction of 1-ethyl-5 : 8-dimethyl-2 : 3-benzopyrrocoline and methyl iodide was effected in the same manner and the resulting salt crystallised from water or ethanol as colourless or pale yellow prisms, m. p. 247—249° (decomp.) (Found: C, 55·9; H, 5·4; I, 35·0%). A mixture with the 7′-ethyl-3 : 6 : 7′-trimethyl-1 : 2-(2′ : 7′)benzylenepyridinium iodide obtained from trimethylbenzopyrrocoline and ethyl iodide had m. p. 247—249° (decomp.). The two specimens were compared by means of *X*-ray single-crystal photographs, for which we are greatly indebted to Mrs. D. Crowfoot Hodgkin and Miss P. M. Cowan. The identity of the two specimens was fully confirmed by their report.

3 : 6 : 7′ : 7′-*Tetramethyl*-1 : 2(2′ : 7′)*benzylenepyridinium iodide* was similarly prepared from the base and methyl iodide and crystallised from water as colourless prisms, with a slight yellow or green tinge, m. p. 239—241° (decomp.) (Found: C, 54·9; H, 5·1; I, 36·3. $C_{16}H_{18}NI$ requires C, 54·7; H, 5·1; I, 36·2%).

The ultra-violet absorption spectra (Fig. 1) show clearly the nuclear-skeletal identity of the three salts studied.

Condensation of Tetramethylbenzylenepyridinium Iodide with p-*Dimethylaminobenzaldehyde.*—An alcoholic solution of the quaternary iodide (1 g.), *p*-dimethylaminobenzaldehyde (0·5 g.), and piperidine (2 drops) was refluxed for an hour. The solvent was then removed and the product crystallised from ethanol or ethanol–ether. 3 : 7 : 7′-*Trimethyl*-6-p-*dimethylaminostyryl*-1 : 2(2′ : 7′)*benzylenepyridinium iodide* was obtained as red, hexagonal prisms, decomp. 209—210° (Found: C, 62·5; H, 6·3; I, 24·3. $C_{26}H_{29}N_2I,\frac{1}{2}C_2H_5{\cdot}OH$ requires C, 62·4; H, 6·2; I, 24·5%).

The quaternary iodide also gave a deep red dye with *p*-nitrosodimethylaniline under the same conditions. The product was obtained as greenish-black plates with a metallic lustre, decomp. 215—216°. When heated in pyridine solution with hydroxylamine hydrochloride the dye was decomposed and an almost colourless solution resulted.

1 : 8-*Dimethyl*-2 : 3-*benzopyrrocoline* (I; R = R′ = Me, R″ = H).—A solution of skatole (3·6 g.) and lævulaldehyde dimethyl acetal (3·6 g.) in ethanol (10 c.c.) was saturated with dry hydrogen chloride at 0°; it was then poured into water (50 c.c.) and shaken with ether. The aqueous layer was basified with sodium hydroxide and kept in the refrigerator. Next day the product was collected and crystallised from light petroleum (b. p. 60—80°) and then twice from ethanol. 1 : 8-*Dimethyl*-2 : 3-*benzopyrrocoline* (2 g.) was obtained as yellow needles, m. p. 86—87° (Found: C, 86·0; H, 6·7; N, 7·0. $C_{14}H_{13}N$ requires C, 86·2; H, 6·7; N, 7·2%).

The *perchlorate* was prepared in acetone and crystallised from methanol as colourless prisms, m. p. 173—176° (Found: C, 56·7; H, 4·8; N, 4·6; Cl, 12·2. $C_{14}H_{13}N,HClO_4$ requires C, 56·9; H, 4·8; N, 4·7; Cl, 12·0%). The "*methiodide*" [3 : 7′ : 7′-*trimethyl*-1 : 2(2′ : 7′)*benzylenepyridinium iodide*] was obtained from water as very pale yellow needles, m. p. 252° (decomp.) (Found: C, 53·6; H, 4·9; I, 38·2. $C_{15}H_{16}NI$ requires C, 53·4; H, 4·8; I, 37·7%). This salt gave no colour when heated in ethanol solution with *p*-dimethylaminobenzaldehyde, showing that there can be no methyl group in the α-position to the nitrogen atom of the pyridine ring.

1-*Ethyl*-8-*methyl*-2 : 3-*benzopyrrocoline* (I; R = Et; R′ = Me; R″ = H).—A solution of 3-ethylindole (2 g.) in methanol (20 c.c.) was saturated with hydrogen chloride. 2-Methylfuran (2 c.c.) was added and the mixture kept for 12 hours. Water (100 c.c.) was added and the neutral material extracted with ether. The base was then isolated as before and purified by way of the perchlorate. 1-*Ethyl*-8-*methyl*-2 : 3-*benzopyrrocoline* (1 g.) was obtained from methanol as golden flakes, m. p. 71—73° (Found: C, 85·8; H, 7·2; N, 6·7. $C_{15}H_{15}N$ requires

C, 86·1; H, 7·2; N, 6·7%). The *perchlorate* was crystallised from water or methanol containing a trace of perchloric acid, and obtained as colourless prisms, m. p. 166—168° (Found: C, 58·0, 58·3; H, 4·9, 5·3; N, 4·7; Cl, 11·4. $C_{15}H_{15}N,HClO_4$ requires C, 58·2; H, 5·2; N, 4·5; Cl, 11·5%). The "*methiodide*" [*7'-ethyl-3 : 7'-dimethyl-1 : 2(2' : 7')-benzylenepyridinium iodide*] was obtained from water as very pale yellow rhombs, m. p. 219—221° (Found: C, 54·8; H, 5·0; I, 36·5. $C_{16}H_{18}NI$ requires C, 54·7; H, 5·1; I, 36·2%). This salt gave no colour on being heated in ethanol solution with *p*-dimethylaminobenzaldehyde and a trace of piperidine.

1-Methyl-2 : 3-benzopyrrocoline (I; R = Me; R' = R'' = H).—Hydrogen chloride was led into a suspension of succindialdoxime (1 g.) in ethanol (20 c.c.) until all the solid had dissolved. A solution of skatole (1 g.) in ethanol (10 c.c.) was then added, and the mixture again saturated with hydrogen chloride and then kept overnight. Water (100 c.c.) was added and the neutral material extracted with ether. The aqueous solution was basified and the product isolated by means of ether and crystallised from methanol. *1-Methyl-2 : 3-benzopyrrocoline* (0·2 g.) was obtained as golden plates, m. p. 67—68° (Found: C, 85·7; H, 6·2; N, 7·7. $C_{13}H_{11}N$ requires C, 86·2; H, 6·1; N, 7·7%).

3 : 7' : 7'-Trimethyl-1 : 2(2' : 7')-benzylenepyrid-6-one (V).—Attempts to oxidize 7'-ethyl-3 : 6 : 7'-trimethyl-1 : 2-benzylenepyridinium chloride, as also its condensation product with *p*-dimethylaminobenzaldehyde, were made using alkaline ferricyanide, potassium permanganate, or hydrogen peroxide. No crystalline product could be isolated. A successful result was achieved only when position 6 was unsubstituted.

An aqueous solution of 3 : 7' : 7'-trimethylbenzylenepyridinium iodide (5·0 g.) was heated with an excess of freshly precipitated silver chloride for an hour on the steam-bath. Potassium ferricyanide (15 g.) in a little water was added to the cooled and filtered solution which was stirred mechanically, and 2N-sodium hydroxide (50 c.c.) added dropwise until the reaction mixture was strongly alkaline. Ether was added, and the stirring continued for another hour. The ethereal layer was separated, the aqueous layer was again extracted with ether, and the combined extracts were dried and evaporated, leaving a pale yellow semi-solid mass (150 mg.). The pyridone could not be crystallised directly; it was triturated with perchloric acid; the *perchlorate* crystallised, from methanol or water containing a little perchloric acid, as colourless prisms (from methanol) or long, colourless needles (from water), m. p. 202—204° when heated moderately rapidly; when slowly heated it decomposed from 185° to 205° (Found: C, 65·3, 65·4; H, 5·4, 5·7; Cl, 6·5, 6·7. $2C_{15}H_{15}ON,HClO_4$ requires C, 65·4; H, 5·6; Cl, 6·5%). The base (1·0 g.) was regenerated from the perchlorate, and crystallised by the careful addition of light petroleum to its solution in dry ether. *3 : 7' : 7'-Trimethyl-1 : 2(2' : 7')-benzylenepyrid-6-one* was so obtained in colourless needles, m. p. 82—83° (Found: C, 80·2; H, 6·6; N, 6·0, 6·2. $C_{15}H_{15}ON$ requires C, 80·0; H, 6·7; N, 6·2%). This substance is readily soluble in most organic solvents; its solution in ethanol fluoresces blue.

N-Chloroacetyl-3-methylindole.—A solution of skatole (5 g.) in ether (50 c.c.) was added to the Grignard reagent from magnesium (2 g.) and ethyl bromide (10 g.) in ether (200 c.c.), and the mixture warmed on the steam-bath until evolution of ethane ceased. The solution was then cooled in ethanol and solid carbon dioxide, and a solution of chloroacetyl chloride (9 g.) in ether (50 c.c.) was added dropwise with vigorous stirring. Stirring was continued while the reaction mixture was allowed to reach room temperature. Water (50 c.c.) was then added, followed by dilute acetic acid (50 c.c.), and mixture stirred until the intermediate had been decomposed. The ethereal layer was separated, washed with sodium hydrogen carbonate solution, and dried ($MgSO_4$), and the solvent removed without heating. The product was crystallised from ethanol or light petroleum (b. p. 60—80°), and *N-chloroacetyl-3-methylindole* (5 g.) obtained as long, colourless needles, m. p. 105° (Found: C, 63·5; H, 4·7. $C_{11}H_{10}ONCl$ requires C, 63·6; H, 4·8%).

This substance gives a magenta Ehrlich reaction, and a deep brown colour with sulphuric acid and sodium dichromate. It is very susceptible to alkaline hydrolysis and an attempt to condense it with ethyl sodioacetoacetate in alcoholic solution led only to the formation of skatole (m. p. 95°; picrate, m. p. 170°).

Condensation of Indole with Lævulaldehyde Dimethyl Acetal.—An alcoholic solution of indole (2 g.) and lævulaldehyde dimethyl acetal (2·5 g.) was saturated with hydrogen chloride at 0° and then kept overnight. The dark amorphous mass, precipitated by addition of water, was dried and extracted with boiling benzene (1 × 50 c.c.; 2 × 25 c.c.), and the benzene solution treated with charcoal and filtered, yielding a pale yellow solution with a green fluorescence. The solvent was removed *in vacuo*, and the product crystallised from benzene. 1-Methylcarbazole was obtained as colourless rhombs, m. p. 121° alone, and 119—121° when mixed

with authentic 1-methylcarbazole of m. p. 119—120°. When it was mixed with 4-methylcarbazole of m. p. 115—116°, the m. p. was 100—105°. The picrate crystallised from benzene as red prisms, m. p. 151—153°, alone and when mixed with the picrate of authentic 1-methylcarbazole (Found: C, 55·6; H, 3·7; N, 13·3. Calc. for $C_{13}H_{11}N,C_6H_3O_7N_3$: C, 55·6; H, 3·4; N, 13·7%).

4-Methyl-1-phenylcarbazole.—A solution of indole (2 g.) and phenacylacetone (3 g.) in ethanol (20 c.c.) was cooled in ice, saturated with hydrogen chloride, and set aside overnight. The solution was then diluted with water and extracted with ether, and the ethereal extracts were dried and evaporated. The residue was dissolved in benzene and purified by adsorption on alumina. Evaporation of the benzene eluate gave a colourless oil, a solution of which in light petroleum (b. p. 40—60°) deposited crystals. *4-Methyl-1-phenylcarbazole* was so obtained as colourless rhombs, m. p. 114—115° (Found: C, 88·3; H, 5·9; N, 5·5. $C_{19}H_{15}N$ requires C, 88·7; H, 5·9; N, 5·5%). The *picrate* separated from methanol as red needles, m. p. 148° (Found: C, 62·0; H, 3·9; N, 11·4. $C_{19}H_{15}N,C_6H_3O_7N_3$ requires C, 61·7; H, 3·7; N, 11·5%).

Some Further Notes.—Skatole does not condense with 1 : 2-dibenzoylethane in cold ethanolic hydrogen chloride. When the mixture was heated, the diketone was dehydrated to diphenylfuran (Perkin and Schloesser, *J.*, 1890, **57**, 954), m. p. 89° (Found: C, 87·3; H, 5·6. Calc. for $C_{16}H_{12}O$: C, 87·3; H, 5·5%). The yield of diphenylfuran was quantitative when hydrogen chloride was passed into a hot saturated solution of dibenzoylethane.

Under the usual conditions skatole and succinonitrile afforded ethyl succinate and diskatole hydrochloride, m. p. 180° (Found: C, 72·9, 72·9; H, 6·6, 6·5; N, 9·8, 9·3; Cl, 12·1, 11·6. Calc. for $C_{18}H_{18}N_2,HCl$: C, 72·4; H, 6·4; N, 9·4; Cl, 11·9%). Oddo and Crippa (*Atti R. Accad. Lincei*, 1924, [v], **33**, I, 51) give m. p. 173°.

An attempted condensation of ethyl indole-3-carboxylate with acetonylacetone in ethanolic hydrogen chloride led to the formation of intractable tar, and no benzopyrrocoline derivative could be isolated.

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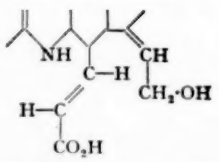
175. *Strychnine and Brucine. Part LII.* Conversion of the Wieland–Gumlich Aldehyde into* iso*Strychnic Acid.*

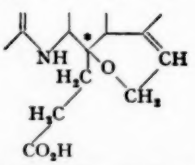
By SIR ROBERT ROBINSON and J. E. SAXTON.

Condensation of the aldehyde, $C_{19}H_{22}O_2N_2$, obtained by the degradation of hydroxyiminostrychnine, with malonic acid in the presence of pyridine and piperidine, affords *iso*strychnic acid. This partial synthesis has a bearing on the problem of the constitution of *iso*strychnic acid.

*iso*STRYCHNIC ACID, $C_{21}H_{24}O_3N_2,H_2O$, was formerly regarded as a *trans*-β-substituted acrylic acid as shown in the partial structure (I) (Oesterlin and Imoudsky, *Ber.*, 1943, **76**, 172; Siddiqui, *J. Indian Chem. Soc.*, 1940, **17**, 152; Leuchs and Schulte, *Ber.*, 1943, **76**, 1038). Because *iso*strychnic acid contains only one aliphatic double bond (dihydro-derivative) and does not contain a hydroxyl group (only an *N*-acyl derivative is obtainable), Leuchs, Mengelberg, and Hemmann (*Ber.*, 1944, **77**, 737; cf. Leuchs and Mengelberg, *Ber.*, 1949, **82**, 250) suggested the structure (II) in which the configuration at the carbon atom marked * differs from that present in strychnine and strychnic acid and is



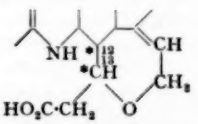
(I)



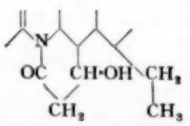
(II)

* Part LI, *J.*, 1950, 1585.

that which occurs in strychninolone-*c*. Finally, Boit (*Ber.*, 1951, **84**, 16) showed that the correct constitution must be (III), in which the configuration of either or both of the carbon atoms marked * (12, 13) is significant.



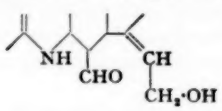
(III)

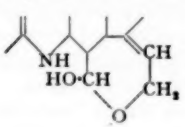


(IV)

The decisive argument concerned the *iso*tetrahydrostrychnine that Leuchs and Schulte had prepared (*loc. cit.*) by the reduction of *iso*strychnic acid in the presence of Adams's catalyst. These authors thought that its facile dehydration indicated a *tert.*-alcoholic structure, but Boit prepared the corresponding *iso*tetrahydrostrychnidine and proved that this was not easily dehydrated. It is therefore, in all probability, a secondary alcohol, and *iso*tetrahydrostrychnine is (IV). The easy dehydration is conditioned by the β-situation of hydroxyl with respect to the carbonyl group.

The structure (III) for *iso*strychnic acid was therefore preferred to (II). At the time of publication of Boit's paper we had independently reached the same conclusion as the result of experiments on the partial synthesis of strychnine. After the discovery of a





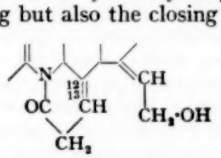
(V)

reactive methylene group in strychnine (benzylidenestrychnine, Perkin and Robinson, *J.*, 1929, 997), Wieland and Gumlich prepared hydroxyiminostrychnine (*iso*nitrososstrychnine) (*Annalen*, 1932, **494**, 191) and degraded it to the aldehyde (or semi-acetal) (V).

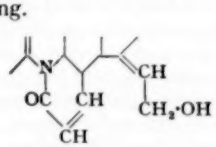
Our project was to reverse this process and build up strychnine from (V), obviously in the first stage by condensation of (V) with acetic acid or a reactive equivalent. This recalls a step in Woodward's theory of the biogenesis of strychnine (*Nature*, 1948, **162**, 155).

After several unsuccessful trials, for example, with acetic anhydride and sodium acetate, it was found that condensation occurred with malonic acid in pyridine solution with the addition of a little piperidine. The product was found to be *iso*strychnic acid, which is strong evidence of the correctness of the structure (III).

It should be pointed out that the term "*iso*strychnic acid" is a misnomer in that it suggests that the substance bears the relation to *iso*strychnine that strychnic acid bears to strychnine. Actually the hydrolysis of *iso*strychnine involves not only the opening of the lactam ring but also the closing of the oxide ring.



(VI)

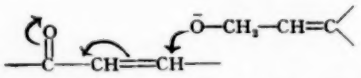


(VII)

Two isomeric *iso*strychnines are known, corresponding in constitution to strychninolones; *iso*strychnine-I ($[\alpha]_D$ +32°) is (VI) and is related to strychninolone-*b*, whilst *iso*strychnine-II ($[\alpha]_D$ −258°) is (VII) and is related to strychninolone-*c* (or, less probably, -*a*). Considering the experimental fact that (VI) yields (III) on treatment with hot alcoholic potassium hydroxide we note that there is no analogy or theoretical basis for the reaction unless it proceeds by initial conversion of *iso*strychnine-I into *iso*strychnine-II or a stereoisomeride of the same structure. The addition of the allylic alcohol to the αβ-unsaturated amide is then understandable; it resembles the transformation of a chalkone into a flavanone (see scheme on p. 984).

But this leads to a further deduction, namely, that in *iso*strychnic acid the configuration at position 12 must be inverted as compared with that in strychnine; for we know that

the configuration of strychninolone-*a* (αβ-double bond) at position 12 is inverted in its transformation into strychninolone-*c* (αβ-double bond) by way of strychninolone-*b* (βγ-double bond).



The problem of the configuration at position 13 in (III) is more difficult. As this asymmetric centre is set up in an additive process to a double bond, adherence to the strychnine configuration would be groundless. A comparison of rotatory powers of relevant substances affords no sure guidance in this case, but inspection of the models suggests that inversion at position 13 should be a corollary of inversion at position 12. Moreover, inversion at position 13 supplies the best explanation of the failure of *iso*strychnic acid to lactamise under any conditions, and this is not only related to the use of models but also to the fact that dihydrostrychninolone-*c* is a stable cyclic amide.

We conclude that *both* centres, 12 and 13, of strychnic acid are inverted in *iso*strychnic acid.

The conversion of the Wieland–Gumlich aldehyde into *iso*strychnic acid is also a conversion into strychnine because Boit (*loc. cit.*) has effected the transformation of *iso*-strychnic acid into *iso*strychnine-1 and Prelog, Battegay, and Taylor (*Helv. Chim. Acta*, 1948, **31**, 2244) have obtained strychnine from *iso*strychnine-I. Under the condition of the experiment it is probable that three *iso*strychnines are equilibrated and only one of these is transformed into strychnine.

We have examined claims that *O*-acyl derivatives of *iso*strychnic acid can be prepared but have not been able to confirm them.

In connexion with the possibility that the Wieland–Gumlich aldehyde is a semi-acetal we place on record the formation of a methyl ether methiodide which probably contains the groups $-CH(OMe)-O-$ and $\dot{N}(b)Me\}I$.

Experimental

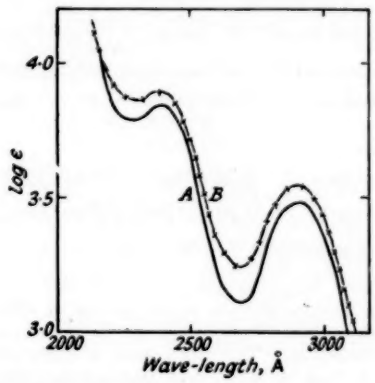
The aldehyde, $C_{19}H_{22}O_2N_2$, was prepared according to the direction of Wieland and Gumlich (*loc. cit.*) and Wieland and Kaziro (*Annalen*, 1933, **506**, 70) and obtained as colourless plates, m. p. 215° (Found: C, 73·8; H, 7·3; N, 8·9. Calc. for $C_{19}H_{22}O_2N_2$: C, 73·6; H, 7·2; N, 9·0%). The *picrate* crystallised from acetone as yellow needles, decomp. 230° (Found: C, 56·0; H, 4·9. $C_{19}H_{22}O_2N_2,C_6H_3O_7N_3$ requires C, 55·7; H, 4·7%). The Wieland–Gumlich aldehyde afforded a hydroxamic acid derivative when heated in aqueous alcohol with benzenesulphohydroxamic acid and sodium carbonate. This gave an immediate deep reddish-purple colour with ferric chloride. The colour is easily distinguished from the strychnidine-type blood-red colour which ferric chloride develops as the result of oxidation of the aromatic amine system in the same molecule, and which requires a few seconds for development in the cold.

Reaction of the Wieland–Gumlich Aldehyde with Malonic Acid.—A mixture of the aldehyde $C_{19}H_{22}O_2N_2$ (3·2 g.), malonic acid (12 g.), pyridine (16 ml.), and piperidine (3 ml.) was heated on the steam-bath until evolution of carbon dioxide ceased. The solvents were removed on the steam-bath under reduced pressure, and the residual gum was taken up in water. The solution was made alkaline with sodium hydroxide, and the mixture of resin and unchanged aldehyde extracted with chloroform. The aqueous solution was neutralised exactly with acetic acid, and the solvent removed under reduced pressure until crystallisation of the amino-acid was observed. When crystallisation was complete, the amino-acid was separated, washed with a little water, and recrystallised from methanolic acetic acid (2·5% of acid). *iso*Strychnic acid (300 mg.) was obtained as colourless prisms, m. p. 244—245° (decomp.) with previous softening from 220°. The exact decomposition point observed depended on the rate of heating.

Authentic *iso*strychnic acid, prepared by Leuchs and Schulte's method (*Ber.*, 1943, **76**, 1038), was obtained from methanolic acetic acid as colourless prisms, decomp. 244—245° with previous softening. Leuchs and Schulte (*loc. cit.*) give m. p. 245—248° (vac.) (decomp.) and Siddiqui (*loc. cit.*) reports m. p. 240° (decomp.). A mixture of the acid prepared from the Wieland–Gumlich aldehyde and authentic *iso*strychnic acid decomposed at 245—250° with previous softening. The behaviour of the two specimens was identical in all respects; both

were easily soluble in dilute acid and alkali, gave a positive ferric chloride reaction, but no Otto reaction; both were slightly soluble in hot water and almost insoluble in the usual organic solvents. The synthetic specimen had $[\alpha]_D^{18}$ −155° in dilute aqueous sodium hydroxide, and authentic *iso*strychnic acid had $[\alpha]_D^{18}$ −152·4°; Leuchs and Schulte (*loc. cit.*) report $[\alpha]_D^{20}$ −151°/d. The ultra-violet absorption spectra of the two specimens have also been compared (see Fig.); within the limits of experimental error they are identical, the small difference being attributable to a variation of concentration. Mrs. D. M. Hodgkin and Miss P. M. Cowan have kindly examined the two specimens by means of powder *X*-ray photographs, and report that they are identical.

Reaction of iso*Strychnic Acid with Benzoyl Chloride.*—The reaction was carried out according to the directions given by Siddiqui (*loc. cit.*). *iso*Strychnic acid (2 g.) was suspended in dry pyridine, and benzoyl chloride (0·9 g.) gradually added. The substance dissolved on shaking, and, on keeping, a crystalline hydrochloride was deposited, which was washed with ether and recrystallised from ethanol, being so obtained as colourless prisms, which softened at 170° and decomposed at 255—257°. After being dried at 100°/15 mm., the compound decomposed at 260° (Found: C, 61·7; H, 6·5; N, 6·8; Cl, 8·5, 8·6. Calc. for $C_{21}H_{26}O_4N_2$,HCl: C, 62·0; H, 6·6; N, 6·9; Cl, 8·7%). The behaviour on heating of authentic *iso*strychnic acid hydrochloride was identical, and the decomposition point was undepressed on admixture of the two specimens.



———— *Authentic* iso*strychnic acid.*
—×—×— iso*Strychnic acid prepared from the Wieland–Gumlich aldehyde.*

The corresponding base, obtained as colourless prisms from methanolic acetic acid, had m. p. 245—250° (decomp.), undepressed on admixture with authentic *iso*strychnic acid (Found: N, 7·5. Calc. for $C_{21}H_{26}O_4N_2$: N, 7·6%).

N-*Acetyliso*strychnic *Acid.*—We followed the directions of Leuchs, Mengelberg, and Hemmann (*loc. cit.*) and converted the product into the perchlorate, which crystallised from water as colourless plates, m. p. 250° (decomp.) with previous frothing at 165—170° (Found: C, 53·5; H, 5·6; N, 5·5. $C_{23}H_{26}O_4N_2$,$HClO_4H_2O$ requires C, 53·8; H, 5·7; N, 5·5%). The free acetyl*iso*strychnic acid gave a positive Otto reaction, but no colour with ferric chloride. This preparation was also carried out according to the conditions given by Siddiqui (*loc. cit.*), but the only product isolated was identical with the above *N*-acetyl*iso*strychnic acid.

Methyl Ester of iso*Strychnic Acid.*—The *dihydrochloride* was prepared by the method of Leuchs, Mengelberg, and Hemmann (*loc. cit.*). It separated from methanol or ethanol as colourless prisms, which lose solvent when kept in an evacuated desiccator and decompose at 215—217° (Found, in dried material: C, 57·9; H, 6·6; N, 5·8; Cl, 15·7. $C_{22}H_{28}O_4N_2$,2HCl requires C, 57·8; H, 6·6; N, 6·1; Cl, 15·5%). The free ester could not be crystallised.

Action of Ethanolic Potassium Hydroxide on iso*Strychnic Acid.*—*iso*Strychnic acid (1 g.) was refluxed for 6½ hours with potassium hydroxide (1 g.) in ethanol (50 ml.). The solvent was removed under reduced pressure and the residue dissolved in an excess of dilute hydrochloric acid. The solution was heated on the steam-bath for an hour, then cooled and made alkaline. No precipitate was obtained, nor did chloroform extract any basic material from the aqueous layer. Under these conditions any strychnic acid produced should have cyclised to

strychnine. On neutralisaton of the aqueous solution, *iso*strychnic acid was quantitatively recovered.

Methyl Ether of Wieland–Gumlich Aldehyde Methiodide.—The alkali-insoluble part of the product from the condensation of the Wieland–Gumlich aldehyde with malonic acid afforded no crystalline material directly. Its reactions suggested the presence of unchanged aldehyde.

A *methiodide*, decomposing above 215°, was obtained by treatment with methyl iodide in methanol and this crystallised from methanol in colourless prisms.

Also a *perchlorate* was prepared in methanolic solution. It was sparingly soluble in methanol and in water and was crystallised from aqueous acetic acid, being so obtained as colourless prisms, decomp. 250° (Found: C, 55·4; H, 5·9; N, 6·0; Cl, 7·7. $C_{20}H_{24}O_2N_2,HClO_4,0{\cdot}5C_2H_4O_2$ requires C, 55·4; H, 5·9; N, 6·2; Cl, 7·8%). These analyses suggested the possibility that the base concerned was the aldehyde methyl ether [–CH(OMe)–O–]. Hence the following experiment was made. A solution of the pure Wieland–Gumlich aldehyde (0·2 g.) in methanol (20 c.c.) containing a drop of 0·1N-hydrochloric acid was refluxed for 20 minutes and evaporated. The glassy residue could not be crystallised but addition of methyl iodide to its methanolic solution gave the above methiodide, decomposing above 215°, as was proved by a careful comparison of the crystals (Found: C, 54·4; H, 5·7; N, 6·0; I, 27·3. $C_{19}H_{22}O_2N_2,CH_3I$ requires C, 53·1. $C_{20}H_{24}O_2N_2,CH_3I$ requires C, 54·1; H, 5·8; N, 6·0; I, 27·3%). A mixture of the two specimens of the methiodide showed no change in the behaviour on heating.

The authors are grateful to the D.S.I.R. for a maintenance grant to one of them (J. E. S.).

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176. *The Chemistry of Fluorene. Part II.* The Dehydration of 9-Hydroxyethylfluorenes.*

By E. J. GREENHOW, D. MCNEIL, and E. N. WHITE.

The dehydration of 9-hydroxyethylfluorenes and 9-ethylfluoren-9-ol by phosphoric oxide in boiling decalin or by activated alumina in the vapour phase yields either ethylidenefluorene or a substituted phenanthrene depending on the conditions. The mechanism of these reactions is discussed and it is suggested that in one case fluorene-9-*spirocyclo*propane is an intermediate. This compound was prepared by the dehydrohalogenation of 9-2′-chloroethylfluorene and proof of its structure is given. 9-Vinylfluorene was not obtained by the dehydration of 9-hydroxyethylfluorenes under the conditions used, and it is suggested that this compound is either incapable of existence or is immediately isomerised.

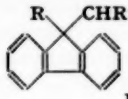
IN Part I * one possible route to 9-vinylfluorene—the condensation of vinyl halides with 9-fluorenylsodium—was mentioned; this reaction resulted in the formation of fluorene, acetylene, and the sodium halide. Dehydration of 9-2′-hydroxyethylfluorene (Part I) offered an alternative route, but it was found that when this compound was passed over activated alumina at 350° or was heated with phosphoric oxide in boiling decalin it yielded products which were at first thought, on the evidence of mixed melting points and mixed melting points of picrates, to be identical with each other and with 9-ethylidenefluorene prepared by dehydration of 9-ethylfluoren-9-ol (Daupresne, *Bull. Soc. chim.*, 1907, **1**, 1236; Ullmann and Wurstemberger, *Ber.*, 1905, **38**, 4107).

It was later shown, however, that although the product obtained by dehydration over alumina was in fact 9-ethylidenefluorene, with an ultra-violet spectrum (Table 3) identical with that of the product obtained from the fluorenol, the dehydration product obtained from the liquid-phase reaction with phosphoric oxide in decalin was 9-methylphenanthrene.

Application of the two methods described above to the dehydration of 9-1′-hydroxyethylfluorene, which had previously been shown to yield 9-ethylidenefluorene on treatment with concentrated hydrochloric acid (Courtot, *Ann. Chim.*, 1915, **4**, 158, 220), gave 9-ethylidenefluorene (alumina at 350°) or a mixture of 9-ethylidenefluorene and 9-methylphenanthrene (phosphoric oxide in decalin).

* Part I, *J.*, 1951, 2848.

The effect of replacement of the remaining $C_{(9)}$-hydrogen atom has been studied; the dehydration results are summarised in the following table.

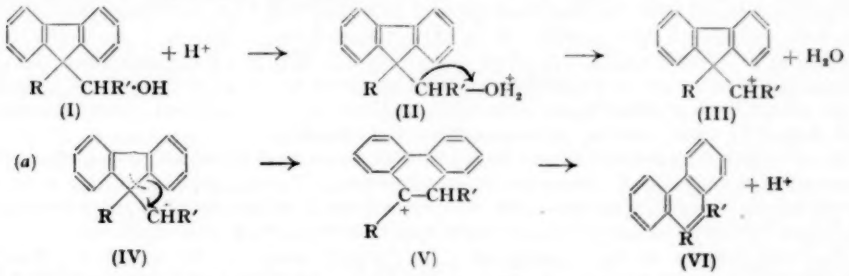


Substituents	Dehydration conditions: Activated alumina at 350°	Dehydration conditions: Phosphoric oxide in boiling decalin or xylene
R = OH; R′ = R″ = H	9-Ethylidenefluorene	9-Ethylidenefluorene
R=R′=H; R″ = OH	9-Ethylidenefluorene	9-Methylphenanthrene
R = R″ = H; R′ = OH	9-Ethylidenefluorene	Mixture of 9-ethylidenefluorene and 9-methylphenanthrene
R = Me; R′ = H; R″ = OH ...	9 : 10-Dimethylphenanthrene	9 : 10-Dimethylphenanthrene
R = Me; R′ = OH; R″ = H ...	9 : 10-Dimethylphenanthrene	9 : 10-Dimethylphenanthrene
R = Et; R′ = OH; R″ = H ...	10-Ethyl-9-methylphenanthrene	

Thus, where there is a free $C_{(9)}$-hydrogen atom vapour-phase dehydration over alumina leads to the production of an ethylidenefluorene whereas the product obtained by use of phosphoric oxide in decalin may be 9-ethylidenefluorene, a substituted phenanthrene, or a mixture of both. Where there is no hydrogen atom on C_9, dehydration by either method is accompanied by the intramolecular change leading to a substituted phenanthrene.

This intramolecular change was first demonstrated by Werner and Grob (*Ber.*, 1904, **37**, 2984) and more clearly by Bachmann (*J. Amer. Chem. Soc.*, 1933, **55**, 3857) who showed that dehydration of 9-α-hydroxybenzyl-9-phenylfluorene yielded 9 : 10-diphenylphenanthrene and not 9-diphenylmethylenefluorene. Brown and Bluestein (*J. Amer. Chem. Soc.*, 1940, **62**, 3256) have prepared phenanthrene by the action of phosphoric oxide on 9-hydroxymethylfluorene and Wittig, Davis, and Koenig (*Ber.*, 1951, **84**, 627) have obtained 9-benzylphenanthrene by the action of phosphorus tribromide on 9-benzyl-9-fluorenylmethanol. We have repeated Brown and Bluestein's experiment and confirmed that 9-hydroxymethylfluorene yields phenanthrene when refluxed with phosphoric oxide in xylene, but when it is passed over alumina at 350° the product is a mixture of 9-methylenefluorene and its polymers, no phenanthrene being detected. 9-Hydroxymethyl-9-methylfluorene was found to undergo rearrangement to 9-methylphenanthrene with both dehydrating agents.

This intramolecular change of a 9-hydroxyalkylfluorene to a phenanthrene derivative is generally regarded as an example of the Wagner rearrangement, proceeding by a mechanism involving a carbonium ion thus :



When R = H the ion (III) may stabilise itself in two ways, either by rearrangement as shown in (*a*), or by the formation of a methylenefluorene (*b*).

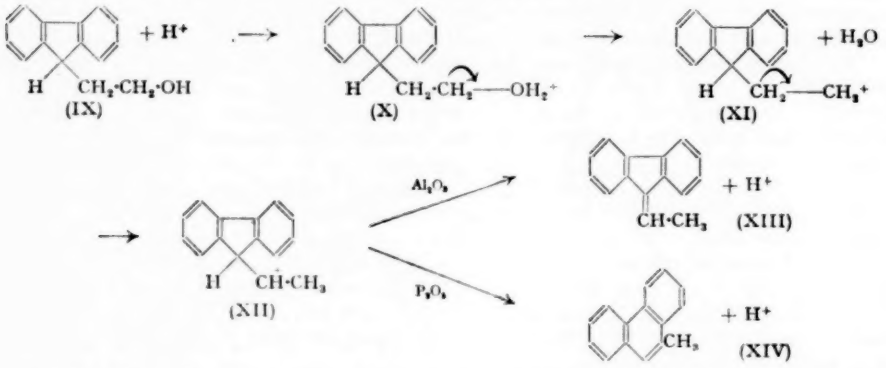
It would be expected that in an alkaline (proton-accepting) environment in which the $C_{(9)}$-hydrogen atom is known to be labile, this second mode of stabilisation would

predominate, and the production of ethylidenefluorene only by the dehydration of 9-1′-hydroxyethylfluorene over alumina and of a mixture of ethylidenefluorene and 9-methylphenanthrene when phosphoric oxide is used is consistent with this view.

To explain the reactions of 9-2′-hydroxyethylfluorene the mechanism shown below (IX—XIV) might be postulated, but in this case one would expect that the products from both hydroxyethylfluorenes when dehydrated in the liquid phase with phosphoric oxide would be the same; no ethylidenefluorene could, however, be isolated from the product obtained from the 2-hydroxyethyl compound.

It is therefore suggested that the ion (XI) formed by proton addition and removal of the elements of water from the 9-2′-hydroxyethylfluorene under the influence of alumina forms the *spirocyclo*propane compound which isomerises to ethylidenefluorene and that, under the more acidic conditions when phosphoric oxide is used, the changes leading to (XIV) from (XI) occur synchronously rather than as distinct stages.

Some support for the view that the *spiro*-compound is an intermediate when 9-ethylidenefluorene is formed from 9-2′-hydroxyethylfluorene is furnished by its ready formation from 9-2′-chloroethylfluorene and its almost quantitative isomerisation to 9-ethylidenefluorene under both sets of dehydration conditions.



The identity of the *spiro*-compound has been established as follows. Analysis shows it to be isomeric with 9-ethylidenefluorene, and its ultra-violet spectrum (Table 3) and the fact that it is oxidised by chromic acid to fluorenone prove it to be a 9-substituted fluorene. Examination of its infra-red spectrum showed no absorption band attributable to either a monosubstituted ethylene (1650 cm.$^{-1}$) or a vinyl group (910 cm.$^{-1}$ and 990 cm.$^{-1}$) (Thompson and Torkington, *Proc. Roy. Soc.*, 1945, *A*, **184**, 3), thus eliminating the only other possible structure, 9-vinylfluorene. Our material agrees in melting point with that produced from 9-methylenefluorene and diazomethane by Wieland and Probst (*Annalen*, 1937, **530**, 274) who, however, gave no evidence of structure.

As a further confirmation it was hoped that bromine would split the *cyclo*propane ring symmetrically to yield 9 : 9-bisbromomethylfluorene. The addition product, however, lost hydrogen bromide spontaneously to form 9-2′-bromoethylidenefluorene [ultra-violet spectrum (Table 3)], which, of course, could also be derived from 9-vinylfluorene.

The replacement of the remaining $C_{(9)}$-hydrogen atom in 9-2′-chloroethylfluorene prevents formation of a *spirocyclo*propane derivative. 9-2′-Chloroethyl-9-methylfluorene is resistant to both dehydrohalogenation and hydrolysis, and is recovered unchanged when heated with potassium hydroxide to 300° or after prolonged refluxing with alcoholic potassium hydroxide. Dehydrohalogenation in the presence of an acid catalyst by Charlton, Dostrovsky, and Hughes's method (*Nature*, 1951, **167**, 986) also did not result in any change. Reaction does take place when the chloro-compound is refluxed in quinoline for several hours, and a small amount of 9 : 10-dimethylphenanthrene can be isolated from the product. The major product, however, appears to be a salt since it is soluble in dilute aqueous acid and not extracted therefrom by chloroform.

It seemed surprising that Courtot (*loc. cit.*) should have obtained 9-ethylidenefluorene from 9-1′-hydroxyethylfluorene under acid conditions (concentrated hydrochloric acid in acetic acid solution), which would be expected to promote the Wagner change. We have therefore repeated Courtot's experiments and, although the time of reaction was increased from 1 to 3 hours, the product obtained contained no picrate-forming material—indicating the absence of both 9-ethylidenefluorene and 9-methylphenanthrene. Chromatography of the oily product gave 9-1′-acetoxyethylfluorene and starting material. The ester on distillation at atmospheric pressure decomposed to acetic acid and 9-ethylidenefluorene. This is in accord with Hurd and Blunck's views (*J. Amer. Chem. Soc.*, 1938, **60**, 2419) that pyrolysis of esters gives rise to the simple dehydration product of the alcohol.

It may be concluded from these results that 9-vinylfluorene is an unstable structure which is either incapable of existence or immediately isomerised under the experimental conditions used.

Experimental

9-Acetylfluorene and 9-Formylfluorene.—These were prepared, in 57% and 80% yield, respectively, by Von and Wagner's methods (*J. Org. Chem.*, 1944, **9**, 155).

9-Hydroxymethylfluorene.—This was prepared from 9-formylfluorene by Brown and Bluestein's method (*J. Amer. Chem. Soc.*, 1940, **62**, 3256). Our product had m. p. 107° (Brown and Bluestein record m. p. 99·5—100°).

9-Ethylfluoren-9-ol.—This was obtained in 78% yield by Ullmann and Wurstemberger's method (*Ber.*, 1905, **38**, 4107).

9-Acyl-9-alkylfluorenes.—9-Acylfluorene (0·1 mole) was added to a cooled solution of sodium (0·1 mole) in dry ethanol (40 c.c.), and alkyl halide (0·11 mole) then slowly added with frequent shaking. The mixture was heated under reflux on a water-bath for 2 hours, the ethanol evaporated *in vacuo*, the residue extracted with ether, and the product obtained by evaporation of the ether from the dried ($MgSO_4$) solution. The following were so obtained: 9-formyl-9-methylfluorene (0·1 mole) [*oxime*, m. p. 175° (Found: C, 81·0; H, 5·9; N, 6·25. $C_{15}H_{13}ON$ requires C, 80·7; H, 5·8; N, 6·3%), and *semicarbazone*, m. p. 227—228° (Found: C, 72·6; H, 5·8; N, 16·1. $C_{16}H_{15}ON_3$ requires C, 72·5; H, 5·7; N, 15·85%)]; 9-acetyl-9-methylfluorene (0·055 mole), m. p. 85—86°, as needles from light petroleum (b. p. 40—60°) [semicarbazone, m. p. 249—250° (cf. Meerwein, *Annalen*, 1913, **396**, 241)]; and 9 acetyl-9-ethylfluorene (0·08 mole), m. p. 70°, as plates from light petroleum (b. p. 40—60° [*semicarbazone*, m. p. 222° (Found: C, 73·5; H, 6·7; N, 14·3. $C_{16}H_{19}ON_3$ requires C, 73·7; H, 6·5; N, 14·3%)].

9-1′-Hydroxyalkylfluorenes.—9-Acylfluorene (0·1 mole) in *iso*propanol (50 c.c.) was heated with a solution of aluminium *iso*propoxide (0·1 mole) in *iso*propanol (50 c.c.) on a water-bath at 85° ± 5°, and the acetone which was formed was distilled off. The residue was cooled, decomposed with cold dilute hydrochloric acid (200 c.c.; 6·5% wt./vol.), and extracted with ether. The product was obtained by evaporation of this dried extract ($MgSO_4$). The following were obtained by this method: 9-1′-hydroxyethylfluorene (0·077 mole), m. p. 103—104°, as needles from light petroleum (b. p. 60—80°) [Courtot (*Ann. Chim.*, 1915, **4**, 159) records m. p. 102—103°]; *9-hydroxymethyl-9-methylfluorene* (0·062 mole), m. p. 148—149°, as prisms from benzene (Found: C, 85·4; H, 6·7%; *M*, 205. $C_{15}H_{14}O$ requires C, 85·7; H, 6·7%; *M*, 210); *9-1′-hydroxyethyl-9-methylfluorene* (0·085 mole), m. p. 81°, as needles from light petroleum (b. p. 60—80°) (Found: C, 85·4; H, 7·0; OH, 7·4%; *M*, 229. $C_{16}H_{16}O$ requires C, 85·7; H, 7·1; OH, 7·6%; *M*, 224); and *9-ethyl-9-1′-hydroxyethylfluorene* (0·076 mole), m. p. 83°, from light petroleum (b. p. 60—80°) (Found: C, 85·3; H, 7·4; OH, 7·5. $C_{17}H_{18}O$ requires C, 85·7; H, 7·6; OH, 7·1%).

9-Methyl-9-sodiofluorene.—9-Methylfluorene (50 g.) and powdered sodamide (11 g.) were heated at 180—190° in decalin (150 c.c.) with stirring for 4 hours in an atmosphere of dry nitrogen. The sodio-derivative separated as a heavy dark oil which cooled to a red solid. This was washed with light petroleum and used immediately in the following preparations. The yield is approximately quantitative.

9-2′-Hydroxyethyl-9-methylfluorene.—9-Methyl-9-sodiofluorene (from 50 g. of 9-methylfluorene) and ethylene chlorohydrin (80 c.c.) were heated under reflux for 6 hours in light petroleum (b. p. 40—60°; 200 c.c.), and the sodium chloride was filtered off. Evaporation of the filtrate *in vacuo* gave *9-2′-hydroxyethyl-9-methylfluorene*, crystallising from benzene in

needles (42·6 g.), m. p. 105—107° (Found: C, 85·3; H, 7·0. $C_{16}H_{16}O$ requires C, 85·7; H, 7·1%).

9-2′-*Chloroethyl*-9-*methylfluorene*.—9-Methyl-9 sodiofluorene (from 50 g. of 9 methylfluorene) was added in portions to a solution of ethylene dichloride (50 g.) in light petroleum (b. p. 40—60°; 300 c.c.), and the mixture heated under reflux for 4 hours, cooled, and filtered to remove sodium chloride. Evaporation of the filtrate gave 9-2′-*chloroethyl*-9-*methylfluorene*, crystallising in needles (67·5 g.), m. p. 100—101°, from *n*-propanol (Found: C, 78·8; H, 6·2; Cl, 14·4. $C_{16}H_{15}Cl$ requires C, 79·0; H, 6·2; Cl, 14·65%).

Fluorene-9-spirocyclo*propane*.—9-2′-Chloroethylfluorene (5 g.) was heated to 200° with potassium hydroxide (1·5 g.) with slow stirring; an exothermic reaction took place and the temperature rose to 270°. Heating was continued for 4 minutes and mixture was then cooled, extracted with water, and acidified (HCl). The oily spiro-*compound* solidified and was crystallised from *n*-propanol, forming needles (3·2 g.), m. p. 71·5° (Found: C, 93·6; H, 6·4%; *M*, 190. Calc. for $C_{15}H_{12}$: C, 93·7; H, 6·2%; *M*, 192). The picrate, prepared in acetic acid, formed orange needles, m. p. 139·5°.

9-2′-*Bromoethylidenefluorene*.—A solution of bromine in carbon tetrachloride (1% vol./vol.; 27·8 c.c.) was added slowly with shaking to one of fluorene-9-*spirocyclo*propane (1 g.) in the same solvent (10 c.c.). The bromine was absorbed in a few minutes, and a small quantity of hydrogen bromide was evolved. The solution, after storage for 20 hours at 0°, was concentrated at 50° (stream of air) to an oil, which, after being boiled with charcoal (1 g.) and light petroleum (b. p. 60—80°; 20 c.c.), crystallised as pale yellow needles, m. p. 90—91° (0·7 g.). The ultra-violet absorption spectrum of this product (Table 3) together with elementary analysis indicates that it was 9-2′-*bromoethylidenefluorene* (Found: C, 66·4; H, 4·15; Br, 28·7%; *M*, 280. $C_{15}H_{11}Br$ requires C, 66·4; H, 4·05; Br, 29·5%; *M*, 276).

9-1′-*Acetoxyethylfluorene*.—(*a*) 9-1′-Hydroxyethylfluorene (1 g.), acetic acid (10 c.c.), and concentrated hydrochloric acid (1 c.c.) were heated under reflux for 3 hours, more concentrated hydrochloric acid (2 c.c.) was added, and heating was continued for 1 hour. The cooled solution was diluted with water and extracted with chloroform; the extract, after being washed with sodium carbonate solution and water, was dried and evaporated. The oily product in benzene was passed through a column (8 in. × ½ in.) of alumina, giving two fractions: (i) 9-1′-*acetoxyethylfluorene* (0·57 g.) as a viscous, non-picrate-forming oil (Found: C, 80·9; H, 6·7. $C_{18}H_{18}O_2$ requires C, 81·2; H, 6·8%), and (ii) 9-1′-hydroxyethylfluorene (0·38 g.), m. p. 104°. Distillation of fraction (i) at atmospheric pressure caused its decomposition to acetic acid and 9-ethylidenefluorene, plates (from ethanol), m. p. and mixed m. p. 104° (picrate, m. p. and mixed m. p. 157—158°). (*b*) 9-1′-Hydroxyethylfluorene (1 g.) and acetic anhydride (10 c.c.) were refluxed for 3 hours, a stream of dry hydrogen chloride being bubbled through the solution. The cooled solution gave 9-1′-acetoxyethylfluorene (0·90 g.) and 9-1′-hydroxyethylfluorene (0·08 g.).

Dehydrations over Activated Alumina at 350°.—The apparatus consisted of an electrically heated hard-glass tube, 16 in. long and 1¼ in. in diameter. This reactor tube, shielded by an outer glass jacket, was clamped vertically and packed with activated alumina (Peter Spence 666, type A, mesh 4—8) to a length of 13 in. A liquid-feed device, controlled by a metal-in-glass needle valve, was fitted to the top of the tube, and a glass receiver, immersed in a solid carbon dioxide–ethanol mixture, connected to the bottom. This receiver was connected through a second outlet, a reflux condenser, and cooling traps to a vacuum gauge and pump.

The compound for dehydration (10 g.) dissolved in benzene (150—500 c.c.) was passed through the alumina, maintained at 350° ± 10°, at approximately 10 c.c./min., at 20 mm. pressure. Results are given in Table 1.

The identity of the dehydration products was established by comparison with known compounds, by comparison of ultra-violet spectra, and by examination of the products of bromination at 0° [1·0 g. of dehydration product in 10 c.c. of carbon tetrachloride was treated with a molecular proportion of bromine in the same solvent (1% v/v); the product was stored for 2 days at 0°, and the residue, obtained by evaporation of the solvent in a stream of air, recrystallised from light petroleum (b. p. 60—80°)].

Dehydrations with Phosphoric Oxide.—The method is that described by Brown and Bluestein (*J. Amer. Chem. Soc.*, 1940, **62**, 3256), except that in certain experiments decalin was used in place of xylene.

The hydroxy-compound (5 g.) was heated with phosphoric oxide (5 g.) and the solvent (20 c.c.); the solvent was decanted, the residual solid washed with light petroleum (b. p. 100—120°). the solvent and washings were evaporated, and the residue was recrystallised from

ethanol, except for 9-1′- and 9-2′-hydroxyethylfluorene where the residue was converted directly, in ethanol, into a picrate, and the picrate, in benzene, decomposed on an alumina column (30 in. × 1 in.). Results are given in Table 2.

TABLE 1.

Fluorene	Product	Yield, g.*	M. p. (mixed m. p.)	
9-Hydroxymethyl-	9-Methylenefluorene	4·1	48—49° (49—50)	Dibromide, m. p. 140—141° (lit., 142—143°); picrate, m. p. 149—151° (lit., 152°).
	Poly-(9-methylenefluorene)	1·4	—	
9 : 1′-Hydroxyethyl-	9-*Ethylidenefluorene*	7·1 †	102—103 (102—104)	(Found: C, 93·5; H, 6·3%; bromine val., 79·8. $C_{15}H_{12}$ requires C, 93·8; H, 6·2%; bromine val., 83·3); dibromide, m. p. and mixed m. p. 93·5°.
9 : 2′-Hydroxyethyl-	9-Ethylidenefluorene	6·8 †	102—103	(Found: C, 93·6; H, 6·1%); dibromide, m. p. 93·5°.
9-Ethyl-9-hydroxy-	9-Ethylidenefluorene	6·9 †	102—103	(Found: C, 93·6; H, 6·2%; dibromide, m. p. 93·5°.
9-Hydroxymethyl-9-methyl-	9-Methylphenanthrene	7·2	92—93 (92—93)	Mixed m. p. with 9-ethylidenefluorene, 95—97°; bromine slowly gives 9-bromo-10-methylphenanthrene, m. p. 121·5—122·5°.
9 : 1′-Hydroxyethyl-9-methyl-	9 : 10-Dimethylphenanthrene	7·0	143—144 (lit., 142·5—143)	(Found: C, 93·0; H, 6·75%; *M*, 208. Calc. for $C_{16}H_{14}$: C, 93·2; H, 6·8%; *M*, 206); picrate, m. p. 196° (lit., 193—194°).
9 : 2′-Hydroxyethyl-9-methyl-	9 : 10-Dimethylphenanthrene	7·2	143—144	(Found: C, 93·1; H, 6·7%;) picrate, m. p. 198°.
9-Ethyl-9 : 1′-hydroxyethyl-	9-Ethyl-10-methylphenanthrene	6·2	85° (lit., 85)	Picrate, m. p. 150° (lit., 150°).

* From 10 g. of the fluorene.

† In the dehydration of 9-1′- and 9-2′-hydroxyethylfluorene and 9-ethylfluoren-9-ol the filtrate after recrystallisation of the products from *n*-propanol gave, on evaporation, viscous oils amounting to approximately 30% of the original yields. The oils contained traces of fluorene and fluorenone which were removed. The filtered oils have not yet been identified; they are not picrate-forming and have negligible bromine values, and infra-red examination indicates that they are identical.

TABLE 2.

Fluorene	Medium *	Time, h.	Product	Yield, g.†	M. p. (mixed m. p.)	Bromination
9 : 1′-Hydroxyethyl	*A*	2	9-Methylphenanthrene; 9-ethylidenefluorene	2·2	93—95°	On addition of bromine in CCl_4, approx. ½ is absorbed rapidly; two products: (*a*) 9-bromo-10-methylphenanthrene (0·53 g.), m. p. 120—120·5°; (*b*) 9-ethylidenefluorene dibromide (0·64 g.), m. p. 92·5—93·5°.
9 : 2′-Hydroxyethyl	*B*	3	9-Methylphenanthrene	2·1	92—93 (92—93)	9-Bromo-10-methylphenanthrene (0·8 g.), m. p. 120—120·5.
9-Hydroxymethyl-9-methyl-	*A*	1	9-Methylphenanthrene	3·0	91—93° (92—93)	9-Bromo-10-methylphenanthrene (0·87 g.), m. p. 120—120·5°.
9 : 1′-Hydroxyethyl-9-methyl-	*A*	2	9 : 10-Dimethylphenanthrene	4·3	143—144 (143—144)	—
9 : 2′-Hydroxyethyl-9-methyl-	*B*	2	9 : 10-Dimethylphenanthrene	4·0	143—144 (143—144)	—

* *A*, xylene at 140—160°; *B*, decalin at 180—190°. † From 5 g. of the fluorene.

The products were identified by the methods indicated above for dehydration over alumina.

Dehydrohalogenation of 9-2′-Chloroethyl-9-methylfluorene.—9-2′-Chloroethyl-9-methylfluorene (3 g.) and quinoline (10 c.c.) were heated under reflux in an atmosphere of nitrogen for 6 hours. The dark product was then distilled at 25 mm. pressure until approximately one-third had distilled, and the combined residue and distillate washed with dilute hydrochloric acid and extracted with chloroform. The washed and dried extract, on evaporation, gave a sticky solid (0·8 g.), which formed a picrate, m. p. 192—196°. Decomposition of this gave 9 : 10-dimethylphenanthrene (0·4 g.), m. p. 143—144°.

9-Bromo-10-methylphenanthrene.—To 9-methylphenanthrene (1 g.) in carbon tetrachloride (10 c.c.) was added a cold solution of bromine (0·83 g.) in carbon tetrachloride (50 c.c.), and the mixture was stored for 2 days at 0°. On evaporation a solid was obtained which crystallised from light petroleum (b. p. 60—80°) in needles (0·93 g.), m. p. 121—122·5° (Found : Br, 28·7. $C_{15}H_{11}Br$ requires Br, 29·5%). *9-Bromo-10-methylphenanthrene* was confirmed by comparison of its ultra-violet spectrum with that of 9 : 10-dimethylphenanthrene.

Absorption Spectra.—Ultra-violet absorption spectra were determined in absolute ethanol, with a Hilger " Uvispek " spectrophotometer. The infra-red absorption spectrum was measured with a modified Hilger D.209 spectrophotometer working as a single-beam instrument, the powdered specimen being suspended in " Nujol."

TABLE 3.—*Absorption spectra.*

9-Ethylidenefluorene	$\lambda_{max.}$, Å	2300	2465	2555	2710	2800	2970	3110				
	log ε	4·61	4·46	4·60	4·13	4·15	4·03	4·00				
9 : 2′-Bromoethylidenefluorene	$\lambda_{max.}$, Å	2280	2520	2610	2790	2870	3120					
	log ε	4·50	4·50	4·61	4·10	4·11	4·14					
9-Methylphenanthrene	$\lambda_{max.}$, Å	2520	2770	2840	2970	3170	3250	3310	3400	3490		
	log ε	4·79	4·13	4·00	4·07	2·5	2·45	2·63	2·41	2·64		
Fluorene	$\lambda_{max.}$, Å	2260 *	2545 *	2610	2710 *	2885	3000					
	log ε	3·86	4·20	4·24	4·10	3·78	3·94					
9-Methylfluorene	$\lambda_{max.}$, Å	2280	2580 *	2650	2730 *	2900	3010					
	log ε	3·80	4·20	4·23	4·11	3·77	3·95					
Fluorene-9-*spirocyclo*propane	$\lambda_{max.}$, Å	2260 *	2590 *	2680	2750 *	2915	3025					
	log ε	4·30	4·15	4·20	4·07	3·90	4·04					
9 : 10-Dimethylphenanthrene	$\lambda_{max.}$, Å	2225	2550	2700 *	2800	2870	3000	3200	3275	3360	3525	
	log ε	4·34	4·75	4·47	4·28	4·05	4·11	2·53	2·40	2·64	2·63	
9-Bromo-10-methylphenanthrene	$\lambda_{max.}$, Å	2240	2560	2725 *	2800	2900	3015	3200 *	3275	3350	3425	3520
	log ε	4·23	4·72	4·35	4·20	4·07	4·10	2·37	2·29	2·40	2·30	2·16

* Inflection.

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177. *The Reactions of Metallic Salts of Acids with Halogens. Part II.* The Interaction of Silver Trifluoroacetate or Silver Perchlorate and Halogens in Various Solvents.*

By R. N. Haszeldine and A. G. Sharpe.

Silver trifluoroacetate and iodine in nitrobenzene yield a solution containing iodine trifluoroacetate, $CF_3 \cdot CO_2I$, or a complex of probable composition $(CF_3 \cdot CO_2)_2AgI$, the product depending on the molecular proportions of the reactants. Iodine trifluoroacetate (trifluoroacetyl hypoiodite) is a powerful iodinating agent by virtue of the " positive " iodine it contains, and iodinates aromatic compounds in the positions expected for attack by an electrophilic reagent. In nitrobenzene, which is only very slightly attacked, iodine trifluoroacetate undergoes thermal decomposition to yield trifluoroiodomethane and carbon dioxide as main products. Re-examination of the interaction of silver perchlorate and iodine in ether leads to the conclusion that there is no evidence for the existence of the chlorine tetroxide postulated by Gomberg (*J. Amer. Chem. Soc.*, 1923, **45**, 398) as a product of this reaction.

Bromine and silver trifluoroacetate form a powerful brominating mixture which at low temperatures reacts by a " positive " bromine mechanism. Uses of these new halogenating agents are indicated.

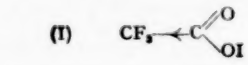
The action of heat on a mixture of silver trifluoroacetate and excess of iodine is represented by the equation $CF_3 \cdot CO_2Ag + I_2 = CF_3I + AgI + CO_2$ (Haszeldine, *Nature*, 1950, **166**, 192; *J.*, 1951, 584). Kleinberg (*Chem. Reviews*, 1947, **40**, 381; where full references are given) has classed reactions between silver salts of carboxylic acids and halogens in two groups: when one mol. of silver salt is treated with one or more mols. of halogen, a compound $R \cdot CO_2X$ is formed, and this undergoes thermal decomposition into RX and carbon dioxide; when, however, two mols. of silver salt are treated in an inert solvent with one mol. of iodine, a complex $(R \cdot CO_2)_2AgI$ is formed, and the action of heat then gives the ester $R \cdot CO_2R$, silver iodide, and carbon dioxide. The present paper gives an account of the interaction of halogens and silver trifluoroacetate in various solvents; and since silver trifluoroacetate, like silver perchlorate, is the salt of a very strong acid and is soluble in benzene and in ether, the bearing of our results on the disputed interpretation of the reaction between silver perchlorate and iodine in ether (Gomberg, *J. Amer. Chem. Soc.*, 1923, **45**, 398; Birckenbach and Goubeau, *Ber.*, 1932, **65**, 395; Gomberg and Gamrath, *Trans. Faraday Soc.*, 1934, **30**, 24; Goodeve, *ibid.*, p. 30; Sidgwick, " The Chemical Elements and their Compounds," Oxford Univ. Press, 1950; Kleinberg, " Unfamiliar Oxidation States and their Stabilization," Univ. Kansas Press, 1950) is considered. We conclude that, as was first suggested by Birckenbach and Goubeau, there is no evidence which requires Gomberg's supposition of the formation of chlorine tetroxide in this reaction.

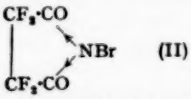
The only inert solvent suitable for quantitative study of the interaction of iodine and silver trifluoroacetate is nitrobenzene. In this solvent, when iodine is shaken with excess of the silver salt, the colour of the iodine disappears, and one mol. of silver iodide is formed from every mol. of iodine. If potassium iodide solution is added, iodine equivalent in quantity to that taken as reactant is liberated, even if the mixture of reaction products is kept at room temperature for 24 hours before determination of the residual oxidising power. The first stage in the reaction is therefore $CF_3 \cdot CO_2Ag + I_2 \longrightarrow CF_3 \cdot CO \cdot OI + AgI$. It appears, however, that iodine trifluoroacetate (trifluoroacetyl hypoiodite) forms a complex with silver trifluoroacetate by a reaction analogous to those between iodine and silver salts of other carboxylic acids: $CF_3 \cdot CO_2Ag + CF_3 \cdot CO \cdot OI \longrightarrow (CF_3 \cdot CO_2)_2AgI$. Hence, when iodine and silver trifluoroacetate are taken in exactly molar proportions in nitrobenzene, less than one mole of silver iodide is precipitated, and the iodine colour persists in the solution; iodine and iodine trifluoroacetate are therefore competing for the silver salt. If the iodine trifluoroacetate is removed, the equilibrium between iodine,

* Part I, *J.*, 1951, 584.

iodine trifluoroacetate, and the complex is disturbed, and precipitation of one mol. of silver iodide is quantitative; this may be effected by addition of phenol, which is very rapidly iodinated by iodine trifluoroacetate at room temperature. Uses of iodine and silver trifluoroacetate as an iodinating mixture in organic chemistry are described below; the high iodinating power makes it impossible to use benzene, ether, or chloroform as a volatile solvent suitable for the preparation and isolation of the iodine trifluoroacetate–silver trifluoroacetate complex (cf. Swarts, *Anal. Soc. Fis. Quim.*, 1929, **27**, 683). The use of trifluoroacetic acid as solvent is prevented by the insolubility of iodine in the acid. Iodine trifluoroacetate and the complex are stable in nitrobenzene for several hours at room temperature, but their isolation from solution cannot be effected: attempts to remove the solvent by distillation produce decomposition (see below).

In iodine trifluoroacetate or the iodine trifluoroacetate–silver trifluoroacetate complex, the powerful inductive effect of the trifluoromethyl group as in (I) will render the iodine more positive than in analogous derivatives of other carboxylic acids. The possession of halogenating powers by iodine or bromine and silver trifluoroacetate is in accord with

(I) 

 (II)

recent work by Henne and Zimmer (*J. Amer. Chem. Soc.*, 1951, **73**, 1103) on positive bromine from perfluoro-*N*-bromosuccinimide (II), which is a more powerful and more specific brominating agent than *N*-bromosuccinimide itself, and is also in accord with the increased positive nature of iodine in trifluoroiodomethane (Banus, Emeléus, and Haszeldine, *J.*, 1951, 60).

Iodine and silver trifluoroacetate as an iodinating mixture are similar to, but less powerful than, the iodine and silver perchlorate mixture described by Birckenbach and Goubeau (*loc. cit.*). Iodine perchlorate and benzene at room temperature react completely within a few minutes, but iodination with iodine and silver trifluoroacetate requires several hours. Iodine trifluoroacetate has, however, important advantages: trifluoroacetic acid, formed by the reaction $RH + CF_3{\cdot}CO{\cdot}OI \longrightarrow RI + CF_3{\cdot}CO_2H$, is volatile (b. p. 71·5°) and is therefore readily removed by distillation; the dangers and by-products attending the use of silver perchlorate (an exceedingly powerful oxidising agent) are avoided; and silver trifluoroacetate is more soluble in organic solvents than silver trichloroacetate, acetate, perchlorate, or sulphate (cf. Derbyshire and Waters, *J.*, 1950, 3694).

Iodination by iodine trifluoroacetate is rapid at higher temperatures, and the following substances have been iodinated (main products are shown in parentheses): benzene (iodobenzene), iodobenzene (*p*-di-iodobenzene), bromobenzene (*p*-bromoiodobenzene), chlorobenzene (*p*-chloroiodobenzene), toluene (*p*-iodotoluene), thiophen (2 : 5-di-iodothiophen), aniline (*p*-iodoaniline), and anisole (*p*-iodoanisole). It should be emphasised that the conditions described in the Experimental section are not necessarily the mildest which can be used; many of the iodinations described will take place more slowly at room or moderate temperatures, and such temperatures can be used if, in a particular instance, the iodinated product would be thermally unstable. For the preparation of simple aromatic iodo-compounds, most of which are thermally stable, the rapid iodination at higher temperatures is more convenient.

The iodination of benzene gave some *p*-di-iodobenzene in yields inversely proportional to the amount of benzene used as solvent. In the iodination of the substituted benzenes mentioned above it is noteworthy that the *p*-iodo-isomer predominates. Small amounts of the *o*-derivative were detected from chlorobenzene and toluene, but in no instance was the *m*-derivative found. The fission of the oxygen–iodine bond in iodine trifluoroacetate can clearly occur by two distinct mechanisms:

(*a*) $CF_3{\cdot}CO{\cdot}OI \longrightarrow CF_3{\cdot}CO{\cdot}O{\cdot} + {\cdot}I$

$\downarrow$

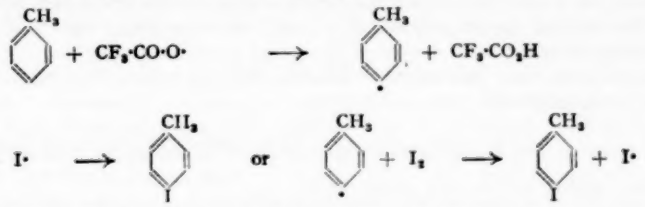
$CF_3{\cdot} + CO_2$

(*b*) $CF_3{\cdot}CO{\cdot}O^-\ I^+ \longrightarrow CF_3{\cdot}CO{\cdot}O^- + I^+$

$\downarrow$

$CF_3^- + CO_2$

If bond fission in iodine trifluoroacetate in solution were by a free-radical mechanism of type (*a*), nuclear iodination would be improbable, since iodine atoms are not known to attack aromatic nuclei; side-chain iodination might occur, but the products of such a reaction were not found in the examples considered. It is unlikely that nuclear iodination is effected by the abstraction of nuclear hydrogen by the $CF_3{\cdot}CO{\cdot}O{\cdot}$ or $CF_3{\cdot}$ radical followed by combination of the resulting radical with iodine, *e.g.*,



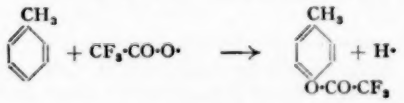
since, in general, free radicals will not abstract nuclear hydrogen from aromatic compounds but will react either by attack on side-chain hydrogen atoms or by substitution in the aromatic nucleus. For the attack of the $CF_3{\cdot}CO{\cdot}O{\cdot}$ radical on toluene, possible products would be :

(1) $Ph{\cdot}CH_3 + CF_3{\cdot}CO{\cdot}O{\cdot} \longrightarrow Ph{\cdot}CH_2{\cdot} + CF_3{\cdot}CO_2H$

$2Ph{\cdot}CH_2{\cdot} \longrightarrow Ph{\cdot}CH_2{\cdot}CH_2Ph$

or

$Ph{\cdot}CH_2{\cdot} + I{\cdot} \longrightarrow Ph{\cdot}CH_2I$

(2) 

cf. $C_6H_6 + C_6H_5{\cdot} \longrightarrow C_6H_5{\cdot}C_6H_5 + H{\cdot}$

The resonance-stabilised benzyl radical when prepared by other routes is known to react mainly by dimerisation : neither dibenzyl nor benzyl iodide was a product of reaction. Fluorine-containing benzene derivatives were not isolated, and, after allowance for handling losses, most of the silver trifluoroacetate was recovered as trifluoroacetic acid.

The *op*-iodination of the compounds studied is in complete accord with iodination by an entity which carries a positive charge, *i.e.*, with ionisation of the type (*b*) above; the compounds concerned contain groups known to activate the aromatic nucleus to electrophilic attack.

Both nitrobenzene and benzoic acid resist attack by electrophilic reagents, and if substitution is to occur at all it will be at the *m*-positions. Nitrobenzene is not affected by iodine trifluoroacetate, and the main products obtained on heating are trifluoroiodomethane and carbon dioxide arising by thermal decomposition, $CF_3{\cdot}CO{\cdot}OI \longrightarrow CF_3I + CO_2$, of the type observed in the absence of a solvent. Benzoic acid in nitrobenzene solution is attacked by iodine trifluoroacetate to yield *m*-iodobenzoic acid [cf. iodine and silver benzoate at 150° which yield *m*-iodobenzoic acid (Birnbaum and Reinherz, *Ber.*, 1882, **15**, 456), presumably *via* $C_6H_5{\cdot}CO{\cdot}OI$ as iodinating agent]. Even if the trifluoroacetoxy-radical were capable of substituting into benzoic acid, then the *p*- and not the *m*-trifluoroacetoxybenzoic acid would be expected, since the *p*-position is favoured for free-radical attack on substituted benzenes. Trifluoroacetoxybenzoic acid and *p*-iodobenzoic acid were not isolated.

The above evidence indicates strongly that iodine trifluoroacetate iodinates in solution by a positive iodine mechanism.

The decarboxylation with simultaneous iodination which occurs when iodine trifluoroacetate is heated in nitrobenzene solution could occur by a free-radical mechanism or, since nitrobenzene is an ionising solvent, by an ionic mechanism : $CF_3{\cdot}CO{\cdot}O^- I^+ \longrightarrow$

$CF_3^- + I^+ + CO_2 \longrightarrow CF_3I + CO_2$. This decomposition would be opposed by the stability of the $CF_3{\cdot}CO{\cdot}O^-$ ion; studies on sodium trifluoroacetate by Auerbach, Verhoek, and Henne (*J. Amer. Chem. Soc.*, 1950, **72**, 299) have shown that the activation energy for the decarboxylation of $CF_3{\cdot}CO{\cdot}O^-$ is 42 kcal. mole^{-1} as compared with 31·6 kcal. mole^{-1} for $CCl_3{\cdot}CO{\cdot}O^-$. This would mean that if iodine trifluoroacetate decomposed by this mechanism, it could be used as an iodinating agent at a higher temperature than iodine trichloroacetate or iodine acetate, as well as being a more powerful agent than either of these. The radical decomposition of iodine trifluoroacetate will clearly be favoured by higher temperatures.

Simonini's reaction (*Monatsh.*, 1892, **13**, 320) by which the ester of the acid under investigation is prepared, *e.g.*,

$$CH_3{\cdot}[CH_2]_n{\cdot}CO_2Ag \xrightarrow{I_2} CH_3{\cdot}[CH_2]_n{\cdot}CO{\cdot}O{\cdot}[CH_2]_n{\cdot}CH_3$$

presumably occurs by an ionic mechanism

$$CH_3{\cdot}[CH_2]_n{\cdot}CO_2Ag + I_2 \longrightarrow CH_3{\cdot}[CH_2]_n{\cdot}CO{\cdot}OI + AgI$$

$$CH_3{\cdot}[CH_2]_n{\cdot}CO{\cdot}O{\cdot}I \longrightarrow CH_3{\cdot}[CH_2]_n{\cdot}I + CO_2$$

$$CH_3{\cdot}[CH_2]_n{\cdot}CO_2Ag + CH_3{\cdot}[CH_2]_n{\cdot}I \longrightarrow CH_3{\cdot}[CH_2]_n{\cdot}CO{\cdot}O{\cdot}[CH_2]_n{\cdot}CH_3 + AgI$$

The predominance of the formation of trifluoroiodomethane (as distinct from the ester, trifluoromethyl trifluoroacetate, by the reaction $CF_3{\cdot}CO_2Ag + CF_3I \longrightarrow CF_3{\cdot}CO{\cdot}O{\cdot}CF_3 + AgI$) when iodine and silver trifluoroacetate are heated alone or in nitrobenzene solution is in accord with the absence of reactions of trifluoroiodomethane which would involve heterolytic fission of the carbon–iodine bond to give CF_3^+ and I^- (Banus, Emeléus, and Haszeldine, *loc. cit.*).

If the ionic mechanism for the Simonini reaction is valid, the last step, $R{\cdot}CO_2Ag + RX \longrightarrow R{\cdot}CO_2R + AgX$, should be facilitated if R is electron-releasing, *e.g.*, if R is an unfluorinated alkyl radical. When R is aromatic, ester formation from RX is much more difficult, and RX and nuclear-halogenated by-products are formed from $R{\cdot}CO_2X$ in proportions depending on the nature of substituents in the nucleus. Silver *m*-methoxybenzoate and bromine in carbon tetrachloride, for example; yield 2-bromo-3-methoxybenzoic acid as the main product (Dauben and Tilles, *J. Amer. Chem. Soc.*, 1950, **72**, 3185). Nuclear bromination by $CH_3{\cdot}O{\cdot}C_6H_4{\cdot}CO{\cdot}OBr$ is apparently the main reaction, and the failure of bromine and silver perchlorate to react with *m*-methoxybenzoic acid under the same conditions (−20°) is probably due to the insolubility of silver perchlorate in carbon tetrachloride, and not to a difference in brominating power between acyl hypobromite and bromine perchlorate.

When R contains an electronegative group such as NO_2, the positive nature of X in $R{\cdot}CO_2X$ and RX will be increased, with further reduction in the amount of ester formed; in addition, the aromatic ring in R will be less susceptible to attack by X^+, and decarboxylation of $R{\cdot}CO_2X$ should become the main reaction. Thus silver *m*-nitrobenzoate and bromine in carbon tetrachloride yield *m*-bromonitrobenzene (68%) as the main product (Dauben and Tilles, *loc. cit.*).

The stoicheiometry of the reaction between bromine and silver trifluoroacetate has not been investigated. These substances when heated together in the absence of a solvent yield bromotrifluoromethane, silver bromide, and carbon dioxide (Haszeldine, *loc. cit.*); in solution, however, they constitute a powerful and useful brominating mixture (cf. Henne and Zimmer, *J. Amer. Chem. Soc.*, 1951, **73**, 1362). Bromination of the following compounds has been effected by a procedure similar to that used with iodine trifluoroacetate: benzene (to bromobenzene), bromobenzene (*p*-dibromobenzene), chlorobenzene (*p*-bromochlorobenzene), toluene (*p*-bromotoluene), anisole (*p*-bromoanisole), aniline (*p*-bromoaniline), and benzoic acid (*m*-bromobenzoic acid). These results are in accord with attack by a positive brominating entity, probably Br^+ from bromine trifluoroacetate. The reactions are similar to those between bromine, silver perchlorate, and organic compounds investigated by Birckenbach and Goubeau (*loc. cit.*), and although bromine per-

chlorate is the more powerful brominating agent, bromine trifluoroacetate has marked advantages similar to those indicated above for iodine trifluoroacetate. Bromine and silver trifluoroacetate react at once in trifluoroacetic acid, and the use of this acid as an inert solvent is being explored.

The conditions recorded in the Experimental section are probably more vigorous than actually required. The bromination of anisole, for example, proceeds steadily at 0°, although the reaction can be hastened by slowly raising the temperature from 20° to 120°. With toluene, product and yield were the same when the reaction was carried out by raising the temperature to reflux as when the reactants were kept at room temperature. The reaction, which clearly occurs rapidly at room temperature, and yields exclusively the *p*-bromo-isomer, undoubtedly involves an ionic mechanism. A radical decomposition of $CF_3{\cdot}CO{\cdot}OBr$ to yield bromine atoms ($CF_3{\cdot}CO{\cdot}OBr \longrightarrow CF_3{\cdot}CO{\cdot}O{\cdot} + Br{\cdot}$) would result in bromination in the side chain (as in bromination by bromine in the presence of heat, peroxides, or light) and not in the nucleus.

When the bromine was added to silver trifluoroacetate in toluene at 110° in the absence of light, nuclear bromination was still the main reaction but some benzyl bromide and small amounts of dibenzyl were formed. These could arise either by the free-radical decomposition of bromine trifluoroacetate to give bromine atoms as above, or by the reaction of bromine with the methyl group of toluene rather than with silver trifluoroacetate.

At higher temperatures, or with compounds which resist ionic halogenation, it may be possible to use bromine trifluoroacetate as a brominating agent analogous to *N*-bromosuccinimide. A chain reaction analogous to that postulated for bromination by the latter reagent can be visualised :

$$CF_3{\cdot}CO{\cdot}O{\cdot} + Ph{\cdot}CH_3 \longrightarrow CF_3{\cdot}CO_2H + Ph{\cdot}CH_2{\cdot} \xrightarrow{CF_3{\cdot}CO{\cdot}OBr} Ph{\cdot}CH_2Br + CF_3CO{\cdot}O{\cdot}$$

$$\downarrow$$

etc.

The competing reaction involving the thermal decomposition of bromine trifluoroacetate to bromotrifluoromethane and carbon dioxide may predominate, however, with compounds less susceptible to radical attack. Reactions with unsaturated compounds such as *cyclo*hexene will be described in a later communication.

The bromination of benzoic acid in nitrobenzene yielded the *m*-derivative; the isolation of *m*-bromonitrobenzene and the evolution of some carbon dioxide without simultaneous formation of bromotrifluoromethane indicated that slight attack on the solvent also took place. Nitrobenzene itself gave a low yield of *m*-bromonitrobenzene; bromotrifluoromethane and unidentified products were also formed.

The evidence presented above shows that in solution the halogen trifluoroacetates (trifluoroacetyl hypohalites) can act as sources of positive halogens, thereby providing powerful and specific halogenating agents.

It was reported by Gomberg (*loc. cit.*) that in ether (though not in other solvents) prolonged interaction of iodine and silver perchlorate proceeds according to the equation $2AgClO_4 + I_2 \longrightarrow 2AgI + 2ClO_4$, yielding a solution of chlorine tetroxide, which is distinguished from perchloric acid by its liberation of iodine from hydrogen iodide. The stoicheiometry, however, and in particular the retention of oxidising power after 2·00 mols. of silver iodide had been precipitated at the end of a slow reaction, were not rigidly established. Birckenbach and Goubeau (*loc. cit.*) suggested the intermediate formation of iodine perchlorate, $AgClO_4 + I_2 \longrightarrow AgI + IClO_4$, followed by iodination of the ether to give an unstable iodo-ether which slowly reacted with the second mol. of silver perchlorate, forming another mol. of silver iodide, $AgClO_4 + RI \longrightarrow AgI + RClO_4$. They found that at the end of the reaction the characteristic oxidising properties claimed for the oxide ClO_4 had vanished, and attributed this to complete consumption of the iodine perchlorate in iodinating the solvent. Later authors have disagreed on the interpretation of the facts without presenting further experimental material: Gomberg and Gamrath (*loc. cit.*) have affirmed their faith in the existence of the tetroxide, and their conclusions have been very

recently accepted by Kleinberg (*loc. cit.*); Goodeve (*loc. cit.*) and Sidgwick (*loc. cit.*) regard its existence as unproven.

Birckenbach and Goubeau showed conclusively that when iodine and silver perchlorate react with an aromatic compound the overall reaction is $C_6H_5X + I_2 + AgClO_4 \longrightarrow C_6H_4XI + AgI + HClO_4$, nuclear iodo-compounds not being affected by the presence of excess of silver perchlorate in ether. Their postulated ready reaction between the iodinated ether and the silver salt could not, however, be verified, owing to the instability of the iodinated ether. Later work by Meyer and Spormann (*Z. anorg. Chem.*, 1936, **228**, 341), however, strongly supports the postulate: alkyl iodides in general react with silver perchlorate in ether at ordinary temperatures, *e.g.*, $C_2H_5I + AgClO_4 \longrightarrow C_2H_5ClO_4 + AgI$. We find that the stoicheiometry of the iodine–silver trifluoroacetate reaction in ether is similar to that for the iodine–silver perchlorate reaction; the first precipitation of silver iodide is followed by a slow secondary precipitation, and much more than one mol. of silver iodide per mol. of iodine is obtained, while the oxidising power of the solution decreases. Reinvestigation of the reaction between iodine and silver perchlorate showed that within thirty minutes of mixing ethereal solutions of iodine and silver salt the weight of silver iodide formed corresponded to 1·4 mols. per mol. of iodine, and part of the oxidising power remained; when, after a few hours, the yield of silver iodide approached 2·0 mols. per mol. of iodine, all of the oxidising power had vanished. Gomberg's assumption that ether is an inert solvent in the reaction is therefore incorrect; and with the demonstration that, for the formation of more than one mol. of silver iodide per mol. of iodine, reaction with the solvent is an essential step, all need for supposing the formation of chlorine tetroxide in the reaction between iodine and silver perchlorate disappears.

Experimental

Materials.—Silver trifluoroacetate, prepared as described earlier (Haszeldine, *loc. cit.*), was purified by ether extraction, and dried *in vacuo* before use. Organic reactants and solvents were carefully purified and dried by standard techniques, and moisture was excluded from all reactions. Silver perchlorate, prepared by Hill's method (*J. Amer. Chem. Soc.*, 1921, **43**, 254), iodine, and bromine were dried over phosphoric anhydride before use.

Interaction of Iodine and Silver Trifluoroacetate in Nitrobenzene.—In nitrobenzene, 0·523 g. (2·07 m.-moles) of iodine yielded with excess of silver trifluoroacetate 0·506 g. (2·14 m.-moles) of silver iodide (filtered on a Gooch crucible, washed with nitrobenzene and acetone, and dried at 120°). In another experiment, a solution of iodine in nitrobenzene completely retained its oxidising power towards potassium iodide 24 hours after addition of the silver trifluoroacetate. Interaction of 0·686 g. (2·70 m.-moles) of iodine and 0·596 g. (2·70 m.-moles) of silver trifluoroacetate yielded 0·470 g. (2·00 m.-moles) of silver iodide, the colour of the iodine persisting in the solution; 0·908 g. (4·10 m.-moles) of silver trifluoroacetate and a five-fold excess of iodine similarly gave 0·735 g. (3·15 m.-moles) of silver iodide. The iodine trifluoroacetate–silver trifluoroacetate complex is therefore not decomposed by iodine to any considerable extent.

When 0·806 g. (3·64 m.-moles) of silver trifluoroacetate and 0·930 g. (3·65 m.-moles) of iodine were allowed to react, the iodine colour again remained in the solution; on addition of 2 g. of phenol it immediately disappeared; the yield of silver iodide was then 0·845 g. (3·60 m.-moles). The titre of a solution of iodine in nitrobenzene was not affected by addition of phenol.

Interaction of Iodine and Silver Trifluoroacetate in Benzene.—A slow attack on benzene at 20° by iodine trifluoroacetate was demonstrated by determining the oxidising activity of a solution containing 0·413 g. (1·62 m.-moles) of iodine and excess of silver trifluoroacetate after 18 hours; this was only equivalent to 1·49 m.-moles of iodine. Evaporation *in vacuo* over silica gel of the filtrate from 0·244 g. (0·96 m.-mole) of iodine and 0·425 g. (1·92 m.-moles) of silver trifluoroacetate yielded a pale yellow residue which had a faint odour of trifluoroacetic acid and liberated iodine from potassium iodide only in the presence of acid (iodine liberated, 0·67 m.-mole). In concentrated solution, therefore, decomposition of the complex or marked attack on the solvent had taken place.

Phenol reacts much faster than benzene with iodine trifluoroacetate, and it was shown that very nearly one mol. of iodine is converted into the reactive iodinating entity by one mol. of silver salt. Solutions of 0·711 g. (3·22 m.-moles) of silver trifluoroacetate and 1·212 g. (4·78

m.-moles) of iodine were mixed, and 5 g. of phenol were added. Determination of the residual iodine (by thiosulphate titrate) after 5 minutes showed 0·430 g. (1·68 m.-moles) to be present; 3·10 m.-moles had therefore yielded 3·10 m.-moles of $CF_3 \cdot CO \cdot OI$ on treatment with 3·22 m.-moles of silver salt.

Interaction of Iodine and Silver Trifluoroacetate in Ether.—When solutions of iodine and silver trifluoroacetate were mixed, an immediate precipitate formed; if this was filtered off and the filtrate set aside, a further precipitate slowly developed. When 0·554 g. (2·18 m.-moles) of iodine and excess of silver salt were left in contact with ether during 6 hours, 0·682 g. (2·90 m.-moles) of silver iodide was precipitated; the filtrate still had oxidising powers equivalent to 0·83 m.-mole of iodine. This formation of much more than one mol. of silver iodide per mol. of iodine taken contrasts sharply with results in nitrobenzene.

Interaction of Iodine and Silver Perchlorate in Ether.—This is a more powerful iodinating mixture than silver trifluoroacetate and iodine: when 0·262 g. (1·03 m.-moles) of iodine was treated in 25 ml. of pure ether with an excess of silver perchlorate, the oxidising power was reduced to 0·057 m.-mole within 30 minutes. From 0·371 g. (1·46 m.-moles) of iodine and excess of the silver salt, no oxidising power remained after 6 hours, 0·658 g. (2·80 m.-moles) of silver iodide then having been precipitated. Addition of potassium iodide 5 minutes after that of silver perchlorate to a solution of 0·286 g. (1·13 m.-moles) of iodine resulted in the liberation of 1·12 m.-moles of iodine; slow attack on the ether therefore takes place under the conditions reported by Gomberg for the preparation of chlorine tetroxide.

Iodination and Bromination Experiments.—The experiments described below were carried out in a 250- or 500-ml. flask fitted with water condenser and rubber tubing connection to liquid-air traps.

Iodination experiments. (i) Benzene. AnalaR Benzene (10 ml.) and silver trifluoroacetate (4·40 g., 0·02 mole) were placed in the flask, heated to boiling, and cooled to room temperature; iodine (5·10 g., 0·02 mole) and AnalaR benzene (10 ml.) were then added. A precipitate of silver iodide appeared immediately. After 1 hour the clear red solution obtained by filtration was heated to 50° during 30 minutes, whereupon a further quantity of silver iodide was precipitated. The benzene solution, which had a strong odour of trifluoroacetic acid, was filtered, shaken with dilute sodium hydroxide solution to remove acid and the slight excess of iodine, washed with water, dried (Na_2SO_4), and distilled to give unchanged benzene, iodobenzene (3·5 g., 85%) (Found: C, 35·5; H, 2·6. Calc. for C_6H_5I: C, 35·3; H, 2·4%), b. p. 85°/15 mm., 190°/763 mm., n_D^{20} 1·620, and *p*-di-iodobenzene (0·1 g., 6%), m. p. 128—129°.

(ii) Iodobenzene. Iodobenzene (12 ml.) and silver trifluoroacetate (4·40 g.) were heated to 100° and cooled to room temperature. Powdered iodine (5·10 g.) was then added, causing an immediate precipitation of silver iodide. The solution was heated rapidly to 160°, cooled to room temperature, and filtered. The liquid-air traps contained only a small amount of trifluoroacetic acid and no trifluoroiodomethane. Distillation of the solution gave: trifluoroacetic acid (1·85 g., 80%), b. p. 71—72°; iodobenzene, b. p. 80°/12 mm., and *p*-di-iodobenzene (5·1 g., 77%), which recrystallised from ethanol as plates, m. p. 128°.

(iii) Bromobenzene. The above experiment was repeated but with bromobenzene and heating to 130°. No trifluoroiodomethane was detected, and trifluoroacetic acid (*ca.* 70% of theory), unchanged bromobenzene, and *p*-bromoiodobenzene (4·0 g., 71%), b. p. *ca.* 250°, m. p. 90—91° (from ethanol), were detected in the products.

(iv) Chlorobenzene. Chlorobenzene, silver trifluoroacetate, and iodine similarly yielded trifluoroacetic acid, unchanged chlorobenzene, and *p*-chloroiodobenzene (2·96 g., 62%) (Found: C, 29·7; H, 1·9. Calc. for C_6H_4ClI: C, 30·2; H, 1·7%), b. p. 224—228°, m. p. 55—56·5° (from ethanol). The crude chloroiodobenzene fraction was semi-solid and consisted mainly of the *p*-derivative. Infra-red spectroscopic examination of the liquid portion revealed the presence of some *o*-derivative.

(v) Thiophen. Benzene (20 ml.; not AnalaR) was heated under reflux for 5 minutes with silver trifluoroacetate (4·40 g.) and cooled to room temperature. Iodine (5·10 g.) was then added, and the mixture kept at room temperature for 1 hour. The silver iodide was removed by filtration, and distillation gave trifluoroacetic acid, benzene, and 2 : 5-di-iodothiophen (Found: C, 14·4; H, 0·9. Calc. for $C_4H_2I_2S$: C, 14·3; H, 0·6%), b. p. 128°/8 mm., white plates, m. p. 41° (from ethanol).

(vi) Toluene. The experiment with AnalaR benzene was repeated but with toluene and 10 minutes' heating under reflux. After filtration, distillation gave *p*-iodotoluene (3·85 g., 88%) (Found: C, 38·7; H, 3·5. Calc. for C_7H_7I: C, 38·5; H, 3·2%), b. p. 210°, m. p. 35°. The infra-red spectrum of the iodotoluene material showed that no *meta*- and only traces of

ortho-derivative were present. A portion of the product, distilled *in vacuo* (to avoid decomposition of any benzyl iodide), gave no reaction with alcoholic silver nitrate or aqueous sodium hydroxide, thereby proving that iodination was exclusively nuclear. The trifluoroacetic acid recovered was 70% of the theoretical amount.

(vii) Anisole. Anisole (20 ml.) was heated to 100° with silver trifluoroacetate (4·40 g.), cooled to room temperature and powdered iodine (5·10 g.) added; silver iodide was immediately deposited. The mixture was heated to 100° for 15 minutes, cooled, filtered, and distilled. Trifluoroacetic acid (65%), unchanged anisole, and *p*-iodoanisole (3·5 g., 75%), b. p. 235—237°, needles, m. p. 50—51° (from aqueous methanol), were isolated.

(viii) Aniline. The last experiment was repeated, but with aniline. After cooling to room temperature the reaction mixture was filtered, washed with aqueous sodium hydroxide, dried, and distilled to yield *p*-iodoaniline (2·25 g., 51%) as a still residue; recrystallised from ethanol, it had m. p. 66—67°. The *N*-acetyl derivative had m. p. 184° (lit., 184°). The acetyl derivative of *o*-iodoaniline (m. p. 60—61°) is reported to have m. p. 109—110°.

(ix) *NN*-Dimethylaniline. This gave a 41% yield of *p*-iodo-*NN*-dimethylaniline, m. p. 80° (from ethanol) (lit., 82°).

(x) Nitrobenzene. Nitrobenzene (25 ml.) was mixed with silver trifluoroacetate (4·40 g.) and iodine (5·10 g.) and heated under reflux. Silver iodide was deposited at room temperature, and at *ca.* 120° a gas was evolved and collected in the liquid-air traps. Examination of the nitrobenzene solution failed to indicate the presence of *m*-iodonitrobenzene, and only a small amount of trifluoroacetic acid was detected. The volatile material consisted mainly of carbon dioxide and trifluoroiodomethane (75% yield) (*M*, 193. Calc. for CF_3I: *M*, 196), but in addition a volatile product still under investigation was isolated.

(xi) Benzoic acid. Benzoic acid (6·0 g.), silver trifluoroacetate (11·2 g.), and iodine (13 g.) were added to nitrobenzene (100 ml.) and the mixture was heated to 150° for 20 minutes. Carbon dioxide and trifluoroacetic acid were observed in the liquid-air trap and were completely absorbed by aqueous alkali. No trifluoroiodomethane was observed. The nitrobenzene solution was heated for recovery of trifluoroacetic acid (3·2 g.) and was then extracted by 5% sodium hydroxide solution. The alkaline solution was filtered from silver iodide and extracted by ether to remove traces of nitrobenzene. Acidification of the alkaline solution with dilute nitric acid caused precipitation of a solid which was taken up in ether. The aqueous solution was extracted by ether. The ether was removed from the combined, dried, ethereal extracts and the residual solid (10·2 g., 84%) was recrystallised from aqueous ethanol, giving *m*-iodobenzoic acid, m. p. 184—185° (Found: C, 33·8; H, 2·1. Calc. for $C_7H_5O_2I$: C, 33·9; H, 2·0%). Infra-red spectroscopic examination of the crude solid product failed to reveal the presence of *o*- or *p*-iodobenzoic acid.

Bromination experiments. (i) Benzene. AnalaR Benzene (10 ml.) and silver trifluoroacetate (4·40 g., 0·02 mole) were heated to reflux and cooled to room temperature. Addition of bromine (3·3 g., 0·02 mole) and AnalaR benzene (10 ml.) caused an immediate precipitation of silver bromide, which, after 1 hour, was removed by filtration. The brown solution, which had a strong odour of trifluoroacetic acid, was then slowly heated (30 minutes) to 50°, cooled, and shaken with dilute sodium hydroxide solution. After being washed with water, the dried benzene solution was distilled to yield benzene, and bromobenzene (2·80 g., 89%), b. p. 51°/23 mm., 154—155°/765 mm., n_D^{20} 1·561. A small amount of higher-boiling material, m. p. 83—85°, was probably crude *p*-dibromobenzene (m. p. 87°), but was not definitely identified as such.

(ii) Iodobenzene. Silver trifluoroacetate (4·40 g.) and iodobenzene (14 ml.) were heated to 100°, and cooled to room temperature. Addition of bromine (3·3 g.) caused immediate precipitation of silver bromide. The solution was heated rapidly to 150°, cooled, and filtered. No bromotrifluoromethane was isolated from the cooled traps. Distillation gave trifluoroacetic acid (1·5 g., 66%), b. p. 70—72°, and unchanged iodobenzene, b. p. 90°/20 mm., and left a residue of *p*-bromoiodobenzene (4·81 g., 85%), m. p. 91—92° after two recrystallisations from ethanol. The *ortho*-derivative was not isolated.

(iii) Bromobenzene. The use of bromobenzene instead of iodobenzene, with conditions as in the previous experiment, yielded *p*-dibromobenzene (3·05 g., 65%) (Found: C, 30·3; H, 2·3. Calc. for $C_6H_4Br_2$: C, 30·3; H, 1·7%), b. p. *ca.* 220°/760 mm.; recrystallised twice from ethanol, it had m. p. 86—87°. Infra-red spectroscopic examination of the liquid obtained by filtration of the dibromobenzene fraction indicated the presence of *o*-dibromobenzene, but a quantitative separation was not attempted.

(iv) Chlorobenzene. This compound similarly yielded *p*-bromochlorobenzene (2·21 g., 58%) (Found: C, 37·2; H, 2·6. Calc. for C_6H_4ClBr: C, 37·6; H, 2·1%), b. p. 194—197°,

m. p. 67° (from ethanol), trifluoroacetic acid (*ca.* 55%), and a small amount of *o*-bromochlorobenzene detected by infra-red spectroscopic examination.

(v) Toluene. Silver trifluoroacetate (4·40 g.) and toluene (10 ml.) after being heated and cooled were treated with bromine (3·3 g.), and the temperature was then raised to cause refluxing for 10 minutes. Filtration and distillation gave trifluoroacetic acid, toluene, and *p*-bromotoluene (3·09 g., 90%) (Found: C, 49·5; H, 4·5; Br, 45·9. Calc. for C_7H_7Br: C, 49·1; H, 4·1; Br, 46·8%), b. p. 183—186°, identical with a genuine specimen on infra-red spectroscopic examination. No side-chain bromination had occurred since there was no reaction of a portion of the crude material distilled *in vacuo* with alcoholic silver nitrate or sodium hydroxide solution. Furthermore, the infra-red spectrum failed to reveal the presence of *o*- or *m*-bromotoluene or of benzyl bromide.

The experiment was repeated with the temperature kept below 20° during and after the addition of bromine. After 1 hour at this temperature, the silver bromide was removed; the solution was then washed with sodium hydroxide solution and water (to remove trifluoroacetic acid), dried, and distilled, to give essentially the same product (91% yield of *p*-bromotoluene).

When the mixture of toluene (10 ml.) and silver trifluoroacetate (4·40 g.) was heated under reflux and shielded from light whilst bromine (3·3 g.) was slowly added by an inlet-tube dipping under the surface of the liquid, unchanged toluene, *p*-bromotoluene (68%), and side-chain brominated compounds were isolated. The yield of these compounds, estimated by their reaction with sodium hydroxide and silver nitrate solutions, was 14%. The *o*- and *m*-bromotoluenes were not formed. Dibenzyl, m. p. 51—52°, identified spectroscopically, was isolated from the reaction mixtures from two such experiments in 3% yield.

(vi) Anisole. Anisole when heated to 120° with silver trifluoroacetate and bromine gave *p*-bromoanisole (2·86 g., 76%) (Found: C, 44·9; H, 4·2. Calc. for C_7H_7OBr: C, 44·9; H, 3·7%), b. p. 110—115°/23 mm., shown to be identical with a known specimen by comparison of infra-red spectra. The yield of *p*-bromoanisole when the reaction was carried out at 0° for 12 hours was 58%.

(vii) Aniline. In a similar experiment the yield of *p*-bromoaniline (Found: C, 41·7; H, 3·6. Calc. for C_6H_6NBr: C, 41·9; H, 3·5%), m. p. 65—66° (*N*-acetyl derivative, m. p. 167°), was 2·12 g. (62%).

(viii) Nitrobenzene. Nitrobenzene, heated with silver trifluoroacetate and bromine as above, yielded *m*-bromonitrobenzene (19%), bromotrifluoromethane (21%), carbon dioxide (41%), and unidentified volatile and high-boiling products.

(ix) Benzoic acid. This compound (6·0 g.), silver trifluoroacetate (11·2 g.), and bromine (9·0 g.) were added to nitrobenzene (100 ml.), and the mixture was heated to 150° for 20 minutes. Carbon dioxide was evolved but no bromotrifluoromethane was observed. After cooling and removal of the trifluoroacetic acid (*ca.* 60%) by distillation, the solution was filtered and extracted by 5% sodium hydroxide solution. The alkaline extracts were combined with the alkaline extracts of the silver bromide and treated with ether to remove traces of nitrobenzene. Acidification and ether-extraction gave, on removal of the dried ether, a crude solid which, after recrystallisation from aqueous ethanol, yielded *m*-bromobenzoic acid (6·12 g., 61% calc. on silver trifluoroacetate) (Found: C, 42·3; H, 2·7. Calc. for $C_7H_5O_2Br$: C, 41·8; H, 2·5%), m. p. 155°, shown to be identical with a known specimen by infra-red spectroscopic examination. There was no indication of *o*- or *p*-bromobenzoic acid, although a small amount (5%) of *m*-bromonitrobenzene was isolated from the nitrobenzene solution.

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178. *The Use of* 3d *Orbitals in Certain Valency States of the Carbon Atom and Other First-row Elements.*

By R. J. Gillespie.

The possibility that carbon and nitrogen utilise their 3*d* orbitals in bond formation in certain molecules is discussed. The conditions are considered under which higher valency states involving these orbitals are formed and it is shown that the promotional energies involved are probably not prohibitively large. On the basis of the assumption that carbon can utilise one or more of its 3*d* orbitals for bond formation under suitable circumstances, the transition state of a bimolecular substitution reaction at a saturated carbon atom, the transition state of a carbonium ion rearrangement, and the electronic structure of certain metal alkyls are discussed in detail. The possibility that other first-row elements also utilise their 3*d* orbitals in bond formation is also briefly considered.

It is usually assumed that the elements of the first period of the Periodic Table cannot expand their outer octets when combining with other atoms, thus utilising their 3*d* orbitals, as these orbitals are supposed to lie at a very high energy level with respect to the 2*s* and the 2*p* orbitals. It is suggested here, however, that the promotional energy involved is not necessarily so large as to make the use of 3*d* orbitals quite impossible, and that in suitable circumstances carbon, and possibly nitrogen, if not other first-row elements, may make some use of these oribtals and thus achieve a covalency of greater than four.

The promotional energy needed to reach various valency states of an atom can in most cases be calculated approximately from spectroscopic data. Such values, however, apply to the free atom and not to the atom in a state of combination. As we shall show later, the values for the free atom and the combined atom may be quite different. Unfortunately we have no direct information about promotional energies for combined atoms.

We shall first calculate the promotional energies needed to reach the quinquevalent state of a free nitrogen atom and a free negative carbon atom C^- and compare them with the promotional energies needed to reach the quinque- and sexa-valent states of phosphorus and sulphur respectively, thereby showing in a rather rough way that the energy involved in the case of carbon is not prohibitive. We can obtain the information we require from spectral data for the nitrogen atom.

We have that

$$N(2s)^2(2p)^3 \longrightarrow N(2s)(2p)^4 \quad \sim 11 \text{ ev} \quad . \; . \; . \; . \; . \; . \; . \quad (1)^*$$

$$N(2s)^2(2p)^3 \longrightarrow N(2s)^2(2p)^2(3d) \quad \sim 12 \text{ ev} \quad . \; . \; . \; . \; . \quad (2)$$

There is no experimental value for the transition

$$N(2s)^2(2p)^3 \longrightarrow N(2s)(2p)^3(3d) \quad . \; . \; . \; . \; . \; . \; . \; . \quad (3)$$

so let us assume as a first approximation that the energy involved is (1) + (2), *i.e.*, 23 ev. This procedure must, however, overestimate the energy of this transition, as (1) involves the energy of repulsion of two electrons in the same 2*p* orbital whereas the summed process (3) does not. Thus our first estimate of 23 ev will probably be too large by several electron-volts. Let us therefore assume process (3) to involve ~20 ev.

The ground state of the negative carbon atom has the configuration $(2s)^2(2p)^3$. If one of the 2*s* electrons is promoted to a 3*d* level, the quinquevalent configuration $(2s)(2p)^3(3d)$ is obtained. We can obtain the energy associated with this promotion by multiplying the value 20 ev obtained above for the analogous promotion in nitrogen by Z'_{C^-2}/Z'_{N^2} where Z'

* The spectroscopic data used in this paper have been taken from "Atomic Energy Levels" by Charlotte E. Moore, Circular No. 467 of Nat. Bureau Stand.

is the effective nuclear charge, *i.e.*, $Z - s$, where s is the screening constant. We have, using Slater's rules,

$$Z'_N = 3{\cdot}9 \text{ and } Z'_{C^-} = 2{\cdot}9$$

Hence we find $\quad C^-(2s)^2(2p)^3 \longrightarrow C^-(2s)(2p)^3(3d) \quad \sim 11$ ev

The electron affinity of the carbon atom is 1 ev, and therefore we have

$$C(2s)^2(2p)^3 \longrightarrow C^-(2s)(2p)^3(3d) \quad \sim 10 \text{ ev}$$

Now the values given above are for the lowest energy terms of the various electronic configurations. Hence the energies of 10 ev obtained for the formation of the $C^-(2s)(2p)^3(3d)$ configuration from the carbon atom in its ground state and of 20 ev for the formation of the $N(2s)(2p)^3(3d)$ configuration from the free nitrogen atom in its ground state apply, strictly, to the lowest energy terms of these configurations. The actual valency states will be linear combinations of all the atomic states with these configurations and would be expected to lie at 2—3 v above the lowest energy state.

The tetrahedral sp^3 valency state of carbon is known to be at 7 ev above the ground state. Hence we may conclude that the additional energy needed to reach the quinquevalent state from the tetrahedral state is very approximately 6 ev. For nitrogen, the additional energy needed to reach the quinquevalent state from the tervalent ground state is of the order 23 ev.

We may now consider the promotional energies associated with the formation of the quinquevalent state of the phosphorus atom from the tervalent state, and the sexavalent state of sulphur from the bivalent state, both these higher valency states being known in stable compounds. For the phosphorus atom we have

$$P(3s)^2(3p)^3 \longrightarrow P(3s)(3p)^4 \quad \sim 8 \text{ ev}$$
$$P(3s)^2(3p)^3 \longrightarrow P(3s)^2(3p)^2(3d) \quad \sim 9 \text{ ev}$$

Hence, adopting the same procedure as for nitrogen, we have

$$P(3s)^2(3p)^3 \longrightarrow P(3s)(3p)^3(3d) \quad \sim 17 \text{ ev}$$

This method overestimates the actual energy involved as explained earlier and a fair estimate for the transition

$$P(3s)^2(3p)^3 \longrightarrow P(3s)(3p)^3(3d)$$

appears to be ~13 ev. Again, this is the energy of formation of the lowest atomic state with this configuration, and the actual valence state may be several volts higher, *i.e.*, ~16 ev.

For the sulphur atom we have

$$S(3s)^2(3p)^4 \longrightarrow S(3s)^2(3p)^5 \quad \sim 9 \text{ ev} \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad (4)$$
$$S(3s)^2(3p)^4 \longrightarrow S(3s)^2(3p)^3(3d) \quad \sim 9 \text{ ev} \quad . \quad . \quad . \quad . \quad . \quad . \quad (5)$$

therefore $\quad S(3s)^2(3p)^4 \longrightarrow S(3s)^2(3p)^2(3d)^2 \quad \sim 18$ ev

hence by the summation procedure employed above

$$S(3s)^2(3p)^4 \longrightarrow S(3s)(3p)^2(3d)^2 \quad \sim 27 \text{ ev}$$

In this case the repulsion term arising from placing an electron in an orbital already containing one electron is involved in both (4) and (5), but with opposite sign, hence to a first approximation no correction is required. An upward correction of several volts will, however, be needed because the valency state of the sulphur atom will be several volts higher than the lowest atomic state of the same configuration. Thus the formation of the sexavalent state of sulphur from the bivalent state involves a promotional energy of approximately 30 ev.

In all cases where an atom has several valency states the energy of formation of the higher states is partly offset by the formation of additional bonds. However, when reasonable values are taken for the energies of formation of these additional bonds it still appears that the actual promotional energies cannot be so great as the above calculations indicate; if they were so great, stable molecules would not be formed by these higher-valency states. Thus, for example, the energy of the reaction

$$PCl_3 + 2Cl \longrightarrow PCl_5$$

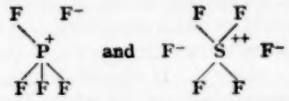
is 78 kcal. (Syrkin and Diatkina, "The Structure of Molecules," Butterworth, London, 1950, p. 261). If we take the energy of formation of the new bonds as a first approximation to be the same as in PCl_3, *i.e.*, 75 kcal. (Syrkin and Diatkina, *op. cit.*), then apparently the actual promotional energy needed to reach the quinquevalent state of phosphorus from the tervalent state is $(2 \times 75) - 78 = 72$ kcal. ~3 ev. This value is to be compared with the value ~16 ev calculated above for the free atom. If we take the value 16 ev for the promotional energy to be correct, then we must assume that the energy of formation of each of the additional bonds is ~10 ev. It seems more reasonable, however, to assume that the energies of formation of the P–Cl bonds are not vastly different in the two cases, and that we must allow for the effect of the presence of the chlorine atoms on the promotional energy needed to reach the quinquevalent state.

The higher valencies of atoms such as phosphorus and sulphur are only stabilised by combination with very electronegative atoms such as fluorine, oxygen, and chlorine, and we can therefore draw the conclusion that the perturbing effect of these atoms on the central phosphorus or sulphur atom is to considerably stabilise (*i.e.*, lower the energy of) their higher (*e.g.*, 3*d*) orbitals or, more accurately, certain combinations or hybrids of these orbitals with lower valency orbitals. When sulphur, for example, combines with a very electronegative atom such as fluorine, the bonds that are formed are polar in the sense $\overset{\delta+}{S}–\overset{\delta-}{F}$. An approximate way of describing this is to say that the bond electrons are occupying a molecular orbital composed of a sulphur atomic orbital that projects strongly in the direction of the fluorine atom and a fluorine atomic orbital that is fairly well localised in the region of the fluorine nucleus. In the case of sulphur hexafluoride the situation is best described in terms of sulphur atomic orbitals by saying that the electrons occupy the six sp^3d^2 hybrid orbitals which project strongly along the six octahedral directions. It is evident that the energy of the electrons in these octahedral orbits will be much lower for the sulphur atom surrounded by six fluorine or other electronegative atoms than for the free sulphur atom, since these electronegative atoms will stabilise the octahedral configuration in which the sulphur electrons are at a relatively large distance from the nucleus.

In general, we may say that the perturbing effect of electronegative atoms on the energy levels of an atom with which they are combined is to lower considerably the energy of certain hybrid orbitals which may involve the participation of orbitals which lie at a relatively high energy level in the free atom. It can be shown by a consideration of the simple case of the hydrogen atom that the perturbing effect of an adjacent positive charge (which is equivalent, of course, to an electronegative atom) is to make the most stable orbital for the hydrogen electron not a pure 1*s* orbital but a 1*s*–2*p* hybrid orbital although the 2*p* orbital lies at 10 ev above the 1*s* (Pritchard and Skinner, *J.*, 1951, 945). These authors remark that "The very significant contribution of the $2p^2$ orbitals to the bonding in H_2^+ and the lesser but nevertheless important contribution in H_2 should be stressed. The relatively large energy separation of the 1*s* and 2*p* atomic orbitals of the H atom is seen to present a barrier insufficient to prevent an appreciable mixing of these orbitals when bond formation occurs. As a consequence, it is reasonable to expect that hybridisation occurs more frequently than not, for in general the energy separations between neighbouring orbitals in atoms other than hydrogen are not larger than in the hydrogen atom itself."

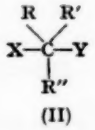
It is perhaps relevant that phosphorus and sulphur are not always regarded as utilising their 3*d* orbitals in the formation of compounds such as phosphorus pentafluoride and

sulphur hexafluoride. It has often been suggested that their structures are resonance hybrids of structures such as

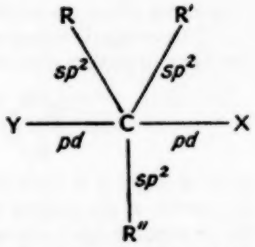


implying that the phosphorus and sulphur atoms make use of their 2*s* and 2*p* orbitals but not of their 3*d* orbitals to form four covalent bonds which resonate among the five or six postions (cf. Pauling, "Nature of the Chemical Bond," Cornell Univ. Press, 2nd Edn., 1940, p. 93). This does not, however, seem to be a completely satisfactory representation of the electronic structure of the molecules as it implies a complete delocalisation of the bonding electrons, whereas by assuming the participation of a *d* orbital in the bonding we retain the idea of a localised bond. A better description of the phosphorus pentafluoride molecule would appear then to be that given above, which in "resonance language" may be considered as a resonance hybrid of the above ionic structures and *in addition* the covalent structure (I) in which the phosphorus atom utilises five orbitals for bond formation, one of which remains empty in each of the ionic structures. One of these five orbitals must be a 3*d* orbital.

(I)



(II)



(III)

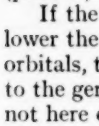
Thus we have seen that the promotional energies involved in the formation of the higher-valency states of the free phosphorus and sulphur atoms are very large and that the energies associated with the use of 3*d* orbitals by nitrogen and carbon are only of the same order. It has been pointed out that these higher-valency states are only found in combination with very electronegative atoms and an explanation for this has been given. It does not seem unreasonable therefore to suggest that in similar circumstances carbon and nitrogen may be able to use 3*d* orbitals in bond formation. We shall show that the assumption that carbon can do so leads to a more satisfactory description than is given by current formulations of the transition state of a bimolecular substitution reaction at a saturated carbon atom, the transition state of a carbonium ion rearrangement, and the electronic structure of certain metal alkyls. The possibility that nitrogen is quinquevalent in some of its compounds is also further discussed.

The Transition State of a Bimolecular Substitution at a Saturated Carbon Atom.—It is suggested that the transition state of a bimolecular substitution reaction at a saturated carbon atom can be satisfactorily described as an unstable compound of quinquevalent carbon. We imagine that the carbon atom is using five orbitals for bond formation, one 2*s*, three 2*p*, and one 3*d*. In contrast to the current resonance picture of the transition state all five atoms or groups are to be regarded as attached to the central carbon atom by ordinary electron-pair bonds. In a completely symmetrical case where all five attached atoms or groups are identical the carbon orbitals will hybridise to form $5sp^3d$ hybrids. However, in the usual case, *e.g.*, (II) where R, R′, and R″ are H or alkyl groups and X and Y are electronegative atoms or groups (*e.g.*, OH, Cl, or F), it seems more likely that the CRR′R″ bonds will be changed merely from tetrahedral sp^3 bonds in the initial state to trigonal sp^2 bonds in the transition state, while the *d* orbital will be shared between the polar C–X and C–Y bonds, which will be formed from two collinear *pd* hybrids on the carbon atom (see III). The carbon atom has a formal negative charge but its actual charge will be very small as the highly projecting *pd* orbitals will cause most of the charge to be in the region of the X

and Y atoms. The nature of these *pd* hybrid orbitals is further discussed in the Appendix (p. 1012).

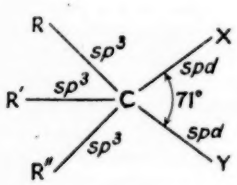
If the presence of the two electronegative atoms or groups, X and Y, can sufficiently lower the energy of the two *pd* hybrid orbitals involving the use of the carbon 3*d* atomic orbitals, then this appears to be a satisfactory description of the transition state alternative to the generally accepted resonance theory. It should be emphasised perhaps that we are not here considering a stable compound but one for which the promotional energy needed to reach the quinquevalent state is not quite counterbalanced by the energy gained from the formation of a new bond. The difference between these two energy values corresponds to the activation energy of the reaction, that is, the energy of formation of the transition state.

An alternative description of the transition state (IV) is apparently possible. However, the fact that inversion of configuration invariably accompanies substitution shows, as is well known, that (III) is actually more stable than (IV). That this should be so is not immediately obvious, as any permutation of the five atoms or groups among the five trigonal bipyramidal postions will minimise filled orbital repulsions. Hence, to a first approximation at least (IV) should have the same energy as (III). Electrostatic repulsions may be of some importance and in the case, for example, where C–X and C–Y are both highly polar in the same sense we might expect that (III) would be a more stable arrangement than (IV). Electrostatic interactions are, however, not the determining factor as is shown by the fact that inversion occurs in the case :

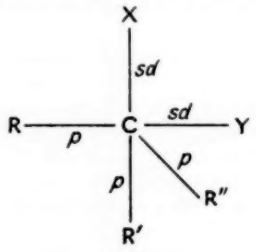


(IV)

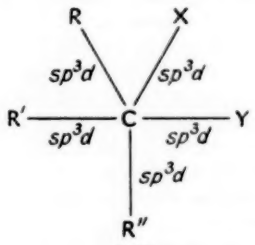
In the hope of gaining a little more insight into the problem let us now examine more closely the nature of the orbital that the central carbon atom uses in the two cases. It is reasonable to assume that the strength and nature of the CRR′R″ bonds will be little altered in the formation of the transition state. They will therefore be formed either from sp^3 orbitals of the central carbon atom or from orbitals with a similar bond-forming power. In configuration (III) the CRR′R″ bonds have been described as being formed from trigonal sp^2 hybrids on the central carbon. It is known that these form bonds of a strength similar to, or slightly greater than, sp^3 hybrids. The weaker and polar C–X and C–Y bonds are formed from two collinear *pd* hybrid orbitals. In configuration (IV) the CRR′R″ bonds cannot be planar trigonal hybrids, and it seems most reasonable to assume



(V)



(VI)



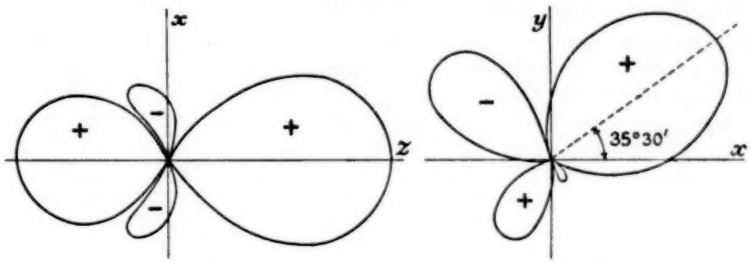
(VII)

that they will be little changed from the initial state, being formed from approximately sp^3 tetrahedral hybrids. This leaves one sp^3 orbital to be hybridised with an appropriate 3*d* orbital to form two equivalent orbitals to be used in bond formation with X and Y. It can be shown (see Appendix) that two orthogonal and normalised orbitals may be formed that are quite strongly directed along two axes at 71° to each other. Hence they will form two polar C–X, C–Y bonds at an angle of approximately 71°. Thus configuration (IV) for the transition state may be more exactly represented by (V). The angle between the C–X and C–Y bonds may only be increased by increasing the amount of s character in the orbitals

forming these bonds and thus appreciably decreasing the strength of the CRR'R'' bonds. In the limiting case where $\angle XCY = 90°$ there are two alternative but equally unsatisfactory descriptions of the transition state. In one case the CRR'R'' bonds could be described as pure *p* orbitals which are therefore at right angles, and the C–X and C–Y bonds as two *sd* hybrids also at right angles (VI). In the other case all the bonds may be described as nearly equivalent sp^3d hybrids with a trigonal bipyramidal arrangement (VII). Neither description is satisfactory because in both cases the orbitals forming the CRR'R'' bonds are considerably changed and the bonds correspondingly weakened. It is clear that if the transition state is to have the configuration (IV) it cannot have the symmetrical trigonal bipyramidal arrangement but must have the rather less symmetrical arrangement (V).

We are now in a position to estimate the relative stabilities of (III) and (IV). This will depend primarily on the relative strengths of the C–X and C–Y bonds and the relative magnitude of filled orbital repulsions in the two cases. The strength of the C–X, C–Y

FIG. 1.



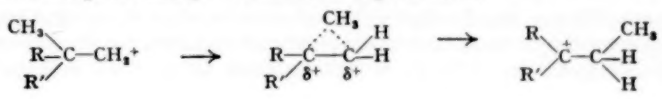
pd hybrid $\psi'_4 = \frac{1}{\sqrt{2}}p_z + \frac{1}{\sqrt{2}}d_z$

spd hybrid $\psi''_4 = \frac{1}{2\sqrt{2}}s + \frac{\sqrt{3}}{2\sqrt{2}}p_x + \frac{1}{2\sqrt{2}}d_{xy}$

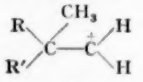
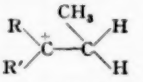
bonds will depend on the overlapping power of the orbitals used by the carbon atom to form these bonds: they are *pd* hybrids for (III) and *spd* hybrids for (IV), as described above and in more detail in the Appendix. Their shapes are shown in Fig. 1.

Without a detailed calculation of overlap integrals, a qualitative consideration of the shapes will serve to convince us that the *pd* orbital used in (III) probably has a better overlapping power than the *spd* orbital used in (IV). The negative portions of the orbital which reduce the effective overlapping ability of the positive portions are relatively larger and more unfavourably situated in the *spd* orbital than in the *pd*. (The largest and most strongly projecting lobe of the orbital which will be responsible for bond formation has been arbitrarily assigned the positive sign in Fig. 1.) Hence we should expect the *pd* hybrid orbital to form rather stronger bonds than the *spd* hybrid. Moreover it is not unreasonable to assume that filled orbital repulsions will be minimised in a symmetrical trigonal bipyramidal arrangement of the transition state and that in any arrangement involving smaller bond angles there may be energetically important repulsions between the atoms concerned. We have seen that configuration (III) may have this symmetrical bipyramidal arrangement, but that configuration (IV) must have a less symmetrical arrangement involving a small bond angle of ~70°. Hence it is not unreasonable to suppose that filled orbital repulsions will be greater in (IV) than (III). Thus we have two reasons for concluding that configuration (IV) will be less stable than (III).

The Transition State of a Carbonium Ion Rearrangement.—Rearrangements in which a methyl or other alkyl group in a carbonium ion migrates from one carbon atom to an adjacent one occur quite readily. This can be represented:



It appears that the transition state of this rearrangement can be more satisfactorily described in terms of the view-point developed in the preceding discussion than in terms of resonance between (VIII) and (IX) according to the current view. This description

(VIII)   (IX)

implies that the migrating methyl group utilises a sp^3 tetrahedral orbital to overlap with orbitals on the two carbon atoms that are presumably nearly pure p orbitals, as shown in Fig. 2. This arrangement of orbitals, however, gives rise to only rather poor overlap and hence rather weak bonds. Thus, if we are to describe the bonds in this transition state in terms of combinations of appropriate atomic orbitals, the sp^3 tetrahedral orbital on the carbon atom of the migrating methyl group would not appear to be suitable for our purpose. An electron on the carbon atom of this methyl group will be strongly attracted by the two adjacent positively charged carbon atoms and will therefore be largely concentrated in two regions of space directed towards these carbon atoms. It will not be suitably described by placing it in a tetrahedral sp^3 orbital. Such an orbital is appropriate

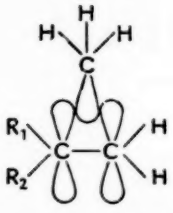
FIG. 2. 

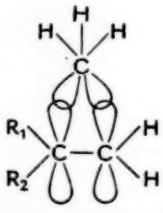
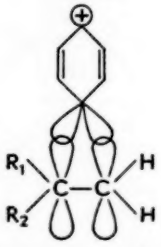
FIG. 3. 

FIG. 4. 

for the description of a bond in the case where a carbon atom is bound to four others, but not when it is bound to five. In the latter case one of the several sets of *spd* hybrids discussed earlier will be more appropriate, in particular that illustrated in (V). The C–H bonds of the migrating methyl group will be formed from tetrahedral sp^3 orbitals, and the carbon atom of the methyl group will be linked to the carbon atom it is leaving and the one it is joining by bonds formed by the overlap of its two hybrid *spd* orbitals at an angle of 70° to each other with p orbitals on the two carbon atoms (Fig. 3). This arrangement of orbitals appears to give better overlap and hence stronger bonds than in the preceding resonance description. The *spd* hybrid orbitals used in this case are stabilised by the presence of the two adjacent positively charged carbon atoms. There are, of course, not sufficient electrons available for both the bonds joining the migrating methyl group to the rest of the molecule to be full electron-pair bonds. To a first approximation there is available only an average of one electron for each of these bonds. However, a small amount of delocalisation of the C–H-bond electrons of the migrating methyl group, which can alternatively be described as a type of hyperconjugation, will lead to an increase in the average number of electrons in these bonds and thus help to increase their strength. It is interesting to note that the transition state for the migration of a phenyl group can be described in a quite similar fashion although, because of the unsaturation of the phenyl group, this does not necessitate the utilisation of a carbon 3*d* orbital. A carbon atom of the migrating phenyl group can utilise two sp^3 tetrahedral orbitals to overlap with the p orbitals on the two adjacent carbon atoms, and the positive charge may be largely accommodated in the phenyl group (Fig. 4). The transition state should therefore be correspondingly more stable and a phenyl should migrate more readily than a methyl group.

The Structure of Certain Metal Alkyls.—The alkyl derivatives of certain metals exist in polymeric forms whose structures have proved difficult to formulate on ordinary valency considerations. Thus, for example, trimethylaluminium forms a stable dimer $Al_2(CH_3)_6$

and dimethylberyllium an infinite linear polymer $[Be(CH_3)_2]_n$. Considerable evidence has accumulated recently that in both these cases the metal atoms are held together by two bridge methyl groups just as two bridge chlorine atoms hold the two aluminium atoms together in Al_2Cl_6 (Longuet-Higgins, *J.*, 1946, 139; Pitzer and Gutowski, *J. Amer. Chem. Soc.*, 1946, **68**, 2204; Kohlrausch and Wagner, *Z. physikal. Chem.*, 1942, *B*, **52**, 185; Rundle, *J. Chem. Physics*, 1949, **17**, 671; Brockway and Davidson, *J. Amer. Chem. Soc.*, 1941, **63**, 3287; Skinner and Sutton, *Nature*, 1945, **156**, 601). We can then write the structure of the alkyl-aluminium and -beryllium polymers as :

where the bridge bonds whose nature is uncertain are indicated by broken lines. Very recently this structure for dimethylberyllium has been fully confirmed by a complete *X*-ray investigation of the solid (Snow and Rundle, *Acta Cryst.*, 1951, **4**, 348).

Various suggestions have been made concerning the electronic structure of these molecules (cf. Longuet-Higgins, *loc. cit.*; *J. Amer. Chem. Soc.*, 1947, **69**, 1327; Davidson, Kingill, Skinner, and Sutton, *Trans. Faraday Soc.*, 1940, **36**, 1212; Skinner and Sutton, *loc. cit.*; Burawoy, *Nature*, 1945, **155**, 269), the most reasonable of which appears to be the resonance formulation,

This implies that an sp^3 orbital on the carbon atom of a bridge methyl is overlapping equally with sp^3 orbitals from each of the aluminium atoms (Fig. 5), forming two localised molecular orbitals each containing two electrons and bonding three nuclei (Al, C, and Al). This does not, however, seem a very satisfactory description of the electronic arrangement; for the overlap of the orbitals oriented in this way cannot be particularly good and would only lead to the formation of rather weak bonds, particularly since there is only an average of one electron available for each Al–C bond in the bridge. Much stronger bonds would be formed if the carbon atoms of the bridge methyl groups could utilise orbitals strongly

FIG. 5.

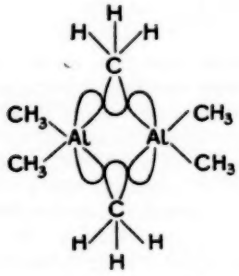
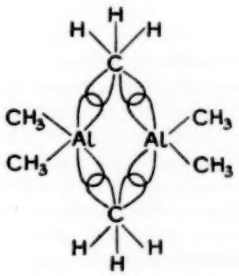
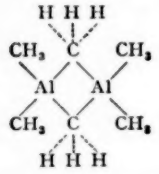


FIG. 6.



directed towards the aluminium atoms. The two *dsp* orbitals described earlier and illustrated in (V) are the orbitals required. If the aluminium orbitals are tetrahedral and therefore $\angle CAlC = 109°$, the $\angle AlCAl$ must be 71° if the ring is assumed to be planar, which is in fact the angle between these two *dsp* hybrids. Good end-on overlap of the carbon *dsp* orbitals and the aluminium tetrahedral sp^3 orbitals can thus be achieved and strong bonds formed. It is suggested therefore that the electronic arrangement of the $Al_2(CH_3)_6$ molecule can best be represented as in Fig. 6. Of course, this and similar

molecules are electron-deficient, and there are not enough electrons for all the bonds to be full electron-pair bonds. In the structure shown above, each of the four bridge bonds contains only one electron. However, a small amount of delocalisation of the C–H bonds of the bridge methyl groups will considerably increase the electron density in the Al–C bonds and hence increase their strength. In fact, if the C–H bonds of the bridge methyl groups are regarded only as 2/3 bonds, then each of the Al–C bonds may be written as a full electron-pair bond, *e.g.*,



The $Be(CH_3)_2$ linear polymer may be formulated similarly (see Fig. 7).

Although recent spectroscopic evidence (Kohlrausch and Wagner, *loc. cit.*) has shown that the bridge structure is almost certainly correct, an early interpretation of the electron-diffraction data (Brockway and Davidson, *loc. cit.*) rejected this type of structure because it predicted a very short Al–Al distance with the ∠CAlC considerably greater than the ∠AlCAl. This is, however, what our formulation requires.

Very recently, from a complete *X*-ray investigation of the dimethylberyllium polymer, Rundle and Snow (*loc. cit.*) have shown that it consists of infinite chains having the structure shown above with ∠BeCBe = 66° and ∠CBeC = 114°, in good agreement with our predictions.

FIG. 7.

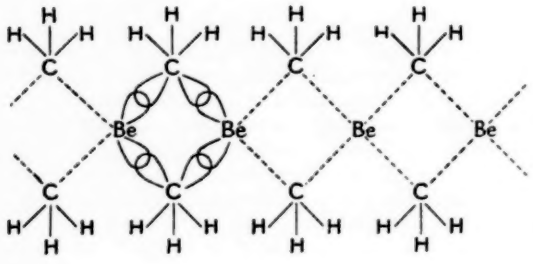
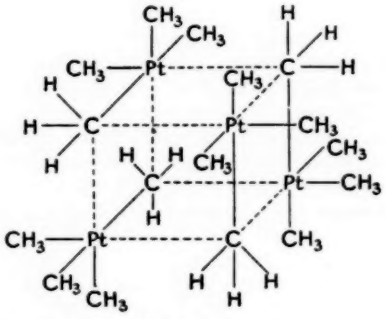


FIG. 8.

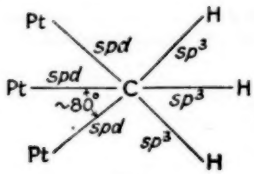


Many aluminium compounds exist in stable polymeric forms and this can be attributed to the very strong tendency of an aluminium atom in a normal tervalent compound to use its empty *p* orbital for bond formation. In the direction of this vacant *p* orbital the aluminium nucleus is very little shielded by the valency electrons and hence *in this direction* the aluminium atom can be regarded as having a very high electronegativity. We should then expect an aluminium atom to pull electrons very strongly into its vacant *p* orbital and, as is well known, the aluminium atom in tervalent aluminium compounds forms a strong bond with any atom that has a lone pair of electrons. Thus in the dimeric aluminium alkyls we should expect that the perturbing effect of the strongly electronegative aluminium atoms on the energy levels of the carbon atoms of the bridge alkyl groups will be to lower the energies of any orbitals that are strongly directed towards the aluminium atoms. The presence of the aluminium atoms makes it easier for the carbon atoms of the bridge alkyl groups to make use of the *dsp* hybrid orbitals. Quite similar considerations apply to the $Be(CH_3)_2$ polymer, the beryllium atom in the monomer having a very strong tendency to utilise its two empty *p* orbitals.

The structure of tetramethylplatinum presents an even greater problem in terms of conventional ideas of valency. An *X*-ray investigation of the solid compound (Rundle

and Sturdivant, *J. Amer. Chem. Soc.*, 1947, **69**, 1561) has shown the presence of tetrameric molecules with the cubic arrangement shown in Fig. 8. The stability of this tetramer can be attributed to the great tendency of quadrivalent platinum to utilise its two empty *d* orbitals and form six octahedral d^2sp^3 bonds. According to the resonance formulation the C–Pt bond formed by the bridge methyl groups can have one of three positions. This implies that the carbon atom of the methyl group is utilising a tetrahedral sp^3 orbital directed along one of the cube diagonals which overlaps equally with a d^2sp^3 octahedral orbital on the platinum atom, thus forming a partly localised molecular orbital containing two electrons and linking together four nuclei. The amount of overlap that can be achieved by the atomic orbitals in this way appears to be very small and unable to lead to strong bond formation, especially since there is only one electron pair available for sharing between three bonds. It would appear that stronger C–Pt bonds would be formed if the carbon atoms of the bridge methyl groups could utilise orbitals more strongly directed towards the platinum atoms. Now when a carbon atom is linked to four other atoms, some form of sp^3 hybrid orbitals is appropriate for bond formation; when it is linked to five other atoms, as in the examples previously discussed, some form of sp^3d hybrid orbital is appropriate for bond formation.

If we assume that the C–H bonds of the bridge methyl groups are formed from unchanged tetrahedral sp^3 orbitals and that the carbon atom can utilise two of its 3*d* orbitals, then three additional equivalent orbitals can be constructed, the angles between these three orbitals being ~80° as shown in the Appendix. They will therefore be suitable orbitals to form bonds with the platinum atoms in the molecule under consideration. Each carbon atom of a bridge methyl group will therefore form bonds as shown in (X). Again we are concerned with an electron-deficient compound and there are available, if we consider all the electrons to be strictly localised in bonds, only two electrons for the three C–Pt bonds formed by one carbon atom. However, this number may be increased by a small amount of delocalisation of the electrons of the C–H bonds of the bridge methyl groups. If we assume that each of these is only a 2/3 bond, then 16 electrons are available for 12 Pt–C bonds which bind together 8 atoms. Thus there is the equivalent of one electron-pair bond per atom, and the stability of the molecule is no longer surprising. The energy of the sp^3d^2 hybrid orbitals used by the carbon atom of the bridge methyl group is lowered sufficiently for these orbitals to be of some importance by the great electronegativity of the surrounding platinum atoms in the directions of their unfilled sp^3d^2 orbitals.



(X)

Quinquevalent Nitrogen.—It seems possible, although perhaps not nearly as probable as for carbon, that nitrogen may sometimes be quinquevalent. The non-existence of compounds with the electronegative halogens such as nitrogen pentachloride can be attributed partly to the rather large promotional energy involved in attaining the quinquevalent state and partly perhaps to steric factors, that is, to considerable repulsions between the five attached atoms. However, although the promotional energy and filled orbital repulsions may be too large to allow the utilisation of *spd* hybrid orbitals for the formation of strong σ-type single bonds, these factors may not prevent the utilisation of these orbitals in the formation of the weaker π-type components of double bonds with oxygen, in compounds where filled orbital repulsions will also be considerably smaller; such a case is nitric acid, for which we might write the structure H–O–N(=O)=O. This formulation implies that the nitrogen atom utilises sp^2 hybrids to form three σ-bonds to oxygen atoms and two *pd* hybrids to form π-bonds to two of the oxygen atoms. There are good reasons for thinking that the oxides and other oxy-compounds of the second-row elements phosphorus and sulphur contain double bonds, and not co-ordinate or semi-polar bonds, as has been accepted for many years, having structures such as O=S(=O)=O and HO–P(=O)(OH)–OH involving the

use of 3*d* orbitals (Hunter, Phillips, and Sutton, *J.*, 1945, 146; Moffitt, *Proc. Roy. Soc.*, 1950, *A*, **200**, 409).

It is difficult to know whether structures involving 3*d* orbitals actually make any important contribution to the structure of oxygen-containing nitrogen compounds, but on the basis of promotional energies alone we cannot state that such structures are of no importance.

Other First-row Elements.—It is unlikely that other first-row elements have a valency shell of more than eight electrons in any of their compounds. In fact, there are exceedingly few compounds in which this is even possible. In a very few compounds oxygen is apparently four-covalent, *e.g.*, "basic" beryllium acetate, $Be_4O(CH_3{\cdot}COO)_6$, and ether complexes of certain alkoxyboron dichlorides [such as $(BCl_2{\cdot}OEt)_2Et_2O$] but it seems rather improbable that it has a valency shell of more than eight electrons even in these compounds. This is, however, not unreasonable as the elements preceding carbon have insufficient electrons unless they acquire improbably large formal negative charges, while the promotional energies associated with the use of 3*d* orbitals in oxygen and fluorine will be even greater than for nitrogen, which, as we have seen, is considerably greater than for carbon.

Appendix

Let us consider the nature of the orbitals that may be formed using one *s*, three *p*, and one *d* orbital. We shall neglect any difference in the radial parts of the wave functions and consider only their angular parts. We have then

$$\psi_s = 1$$
$$\psi_{p_x} = \sqrt{3}\sin\theta\cos\phi$$
$$\psi_{p_y} = \sqrt{3}\sin\theta\sin\phi$$
$$\psi_{p_z} = \sqrt{3}\cos\theta$$
$$\psi_{d_{xy}} = \frac{\sqrt{15}}{2}\sin^2\theta\sin^2\phi$$
$$\psi_{d_z} = \frac{\sqrt{5}}{2}(3\cos^2\theta - 1)$$

Assuming that the orbitals have a trigonal bipyramidal arrangement, we can represent the set of five orbitals by the following wave functions:

$$\psi_1 = \frac{\sin\alpha}{\sqrt{3}}s + \frac{\sqrt{2}}{\sqrt{3}}p_x - \frac{\cos\alpha}{\sqrt{3}}d_z$$
$$\psi_2 = \frac{\sin\alpha}{\sqrt{3}}s - \frac{1}{\sqrt{6}}p_x + \frac{1}{\sqrt{2}}p_y - \frac{\cos\alpha}{\sqrt{3}}d_z$$
$$\psi_3 = \frac{\sin\alpha}{\sqrt{3}}s - \frac{1}{\sqrt{6}}p_x - \frac{1}{\sqrt{2}}p_y - \frac{\cos\alpha}{\sqrt{3}}d_z$$
$$\psi_4 = \frac{\cos\alpha}{\sqrt{2}}s + \frac{1}{\sqrt{2}}p_z + \frac{\sin\alpha}{\sqrt{2}}d_z$$
$$\psi_5 = \frac{\cos\alpha}{\sqrt{2}}s - \frac{1}{\sqrt{2}}p_z + \frac{\sin\alpha}{\sqrt{2}}d_z$$

where α is a variable parameter.

In the special case when $\alpha = \pi$ we have

$$\psi_1' = \frac{1}{\sqrt{3}}s + \frac{\sqrt{2}}{\sqrt{3}}p_x$$
$$\psi_2' = \frac{1}{\sqrt{3}}s - \frac{1}{\sqrt{6}}p_x + \frac{1}{\sqrt{2}}p_y$$
$$\psi_3' = \frac{1}{\sqrt{3}}s - \frac{1}{\sqrt{6}}p_z - \frac{1}{\sqrt{2}}p_y$$
$$\psi_4' = \frac{1}{\sqrt{2}}p_z + \frac{1}{\sqrt{2}}d_z$$
$$\psi_5' = \frac{1}{\sqrt{2}}p_z - \frac{1}{\sqrt{2}}d_z$$

Thus in this case there are three equivalent sp^2 bonds in a plane and two equivalent axial *pd* bonds [cf. (III)]. ψ_4' has been plotted as a polar diagram in Fig. 1. By choice of a suitable value of α, that is by a mixing of *s* and *d* in all five orbitals, they may be made more nearly equivalent than in the above special case, as has been envisaged in (VII).

If, instead of considering the five orbitals to have a regular bipyramidal arrangement, we make the restriction that three of them are tetrahedral sp^3 orbitals, then the set of five orbitals can be represented by the following wave functions.

$$\psi_1'' = \frac{1}{2}s - \frac{1}{2\sqrt{3}}p_x + \frac{\sqrt{2}}{\sqrt{3}}p_z \qquad \psi_4'' = \frac{1}{2\sqrt{2}}s + \frac{\sqrt{3}}{2\sqrt{2}}p_x + \frac{1}{\sqrt{2}}d_{xy}$$

$$\psi_2'' = \frac{1}{2}s - \frac{1}{2\sqrt{3}}p_x - \frac{1}{\sqrt{6}}p_z + \frac{1}{\sqrt{2}}p_y \qquad \psi_5'' = \frac{1}{2\sqrt{2}}s + \frac{\sqrt{3}}{2\sqrt{2}}p_x - \frac{1}{\sqrt{2}}d_{xy}$$

$$\psi_3'' = \frac{1}{2}s - \frac{1}{2\sqrt{3}}p_x - \frac{1}{\sqrt{6}}p_z - \frac{1}{\sqrt{2}}p_y$$

ψ_4'' has been plotted as a polar diagram in Fig. 1. The main maximum of ψ_4'' occurs at $\psi = 35° 30'$, and hence the angle between the directions of the main maxima of ψ_4'' and ψ_5'', and hence between the bonds formed by these orbitals, is 71°, since ψ_5'' is the mirror image of ψ_4'' in the xz plane.

We may also briefly consider the nature of the orbitals that may be formed by use of one s, three p, and two d orbitals with the restriction that three of the orbitals are tetrahedral sp^3 orbitals. We find that the set of six orbitals may be represented by the following wave functions:

$$\psi_1 = \frac{1}{2\sqrt{3}}(s + p_x + p_y + p_z) + \frac{\sqrt{2}}{\sqrt{3}}d_z$$

$$\psi_2 = \frac{1}{2\sqrt{3}}(s + p_x + p_y + p_z) - \frac{1}{\sqrt{6}}d_z + \frac{1}{\sqrt{2}}d_{x-y}$$

$$\psi_3 = \frac{1}{2\sqrt{3}}(s + p_x + p_y + p_z) - \frac{1}{\sqrt{6}}d_z - \frac{1}{\sqrt{2}}d_{x-y}$$

$$\psi_4 = \frac{1}{2}(s + p_x - p_y - p_z)$$

$$\psi_5 = \frac{1}{2}(s - p_x + p_y - p_z)$$

$$\psi_6 = \frac{1}{2}(s - p_y - p_x + p_z)$$

The angle between the three orbitals, ψ_1, ψ_2, and ψ_3, will be equal and between 71° and 90°, *i.e.*, ~80°.

The author acknowledges helpful criticisms by Professor C. A. Coulson and many valuable discussions with Dr. D. P. Craig and Dr. Allan Maccoll.

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179. *The Kinetics of Halogen Addition to Unsaturated Compounds. Part XXII.* Alkyl- and Halogenoalkyl-ethylenes.*

By P. W. Robertson, J. K. Heyes, and B. E. Swedlund.

The rates of bromine addition to the following ethylenic hydrocarbons in acetic acid solution have been measured: *n*-butyl-, *tert.*-butyl-, *neo*pentyl-, and 1-ethyl-1-methyl-ethylene, *cyclo*pentene, *cyclo*hexene, camphene, and α-methylstyrene. Compounds of the type $CRR':CH_2$ and $CHR:CHR'$ (R = *n*-alkyl), including the *cyclo*alkenes, react more rapidly than do $CHR:CH_2$ by a factor of 30—40. *tert.*-Butylethylene is slightly less reactive than *n*-butylethylene, and *neo*pentylethylene is some ten times less reactive still. The rate for allyl fluoride shows that the order in the series, fluoride > chloride > bromide, is contrary to that expected from consideration of the inductive effects of the halogens. The theories relating to these various reactions are discussed.

Kinetic investigations of addition of bromine to ethylenic hydrocarbons involve certain difficulties. Since the lower members are gases at ordinary temperatures and react very rapidly with bromine in acetic acid, modifications of the usual technique are necessary. The purity of the higher liquid homologues must be specially checked, as the methods of preparation frequently give mixtures of isomers.

Experimental

We are indebted to the American Petroleum Institute Research Project 45, a function of the Ohio State University Research Foundation, Columbus, Ohio, U.S.A., for a gift of purified samples of *n*-butylethylene (hex-1-ene) (b. p. 63·5°/760 mm., d_4^{20} 0·6733, n_D^{20} 1·3880), *tert.*-butylethylene (3 : 3-dimethylbut-1-ene) (b. p. 41·2°/760 mm., d_4^{20} 0·6530, n_D^{20} 1·3760), and 1-ethyl-1-methylethylene (2-methylbut-1-ene) (b. p. 31·1°/760 mm., d_4^{20} 0·6584, n_D^{20} 1·3778). Other compounds used in this investigation included *neo*pentylethylene (4 : 4-dimethylpent-1-ene),† b. p. 71·9°/760 mm., n_D^{25} 1·3909, allyl fluoride (prepared by Meslans's method, *Compt. rend.*, 1890, **111**, 882; evaporated through a calcium chloride tube from a mixture of powdered silver nitrate and mercurous fluoride into acetic acid, and standardised by bromine addition, and by reaction with hypochlorous acid acidified with hydrochloric acid),† α-methylstyrene, b. p. 160°/755 mm., *cyclo*hexene, b. p. 81·6—82·6°/750 mm., and *cyclo*pentene, b. p. 43·4°/750 mm.

The solvents and methods were as previously described (cf. *J.*, 1947, 630), and the results, except where otherwise stated, refer to reactions in acetic acid at 25°. The rapidly reacting compounds were examined at M/1000-concentration, at which the reaction proceeds by second-order kinetics ($-d[Br_2]/dt = k[A][Br_2]$), with only a small incursion of the third-order mechanism (*J.*, 1939, 1515). The bromine solution was contained in a tube with a fragile bulb, which was broken in a solution of the other reactant, with rapid agitation of the mixture by the broken tube. The reaction was stopped at about $x = 50\%$ absorption of bromine by rapid addition of potassium iodide solution, the time being measured by a second observer with a stop-watch. Five or six measurements were made at approximately the same time interval, and the bimolecular rate coefficient (k_2, l. mole^{-1} min.$^{-1}$) was estimated from the average of these measurements. Independent observers, using slightly different techniques for preparing the solutions of the hydrocarbons, obtained the following values of $k_2 \times 10^{-3}$: 1·0, 1·1 for *n*-butylethylene; 0·74, 0·65 for *tert.*-butylethylene. The influence of lithium chloride and lithium bromide on the rate of addition to *tert.*-butylethylene was examined. With M/1000-reactants and M/100-lithium chloride, the rate was increased by a factor of 2·7; with M/100-lithium bromide, the rate was reduced by a factor of 1·7. The acceleration with added lithium chloride is probably a salt effect, which is obscured, when lithium bromide is added instead, by the removal of bromine as the less reactive lithium tribromide.

* Part XXI, *J.*, 1950, 2838.

† For the preparation and rate measurements on these two compounds, we are indebted to Professor E. D. Hughes, D.Sc., F.R.S., and his co-workers.

The rates for the still more rapidly reacting compounds are less accurate, as the times for 50% reaction are very small, and the agreement between the results of separate observers is less good. The following are average times (minutes) for 50% reaction, with M/1000-reactants: 1-ethyl-1-methylethylene, 0·030; *cyclo*hexene, 0·036; *cyclo*pentene, 0·025; α-methylstyrene, 0·036.

The following are the results for the more slowly reacting compounds.

0·0017M-*neo*Pentylethylene + 0·0010M-bromine: $x = 20$, $t = 1·1$; $x = 50$, $t = 3·7$.

M/80-Allyl fluoride + M/80-bromine; $x = 10$, $t = 2·4$; $x = 20$, $t = 6·8$; $x = 50$, $t = 30·8$; +M/25-LiCl, $x = 20$, $t = 1·5$.

The earlier value for allyl chloride was confirmed.

Discussion

(a) *Compounds* $CHR{:}CH_2$.—The following results were obtained:

Compound:	$Bu^n{\cdot}CH{:}CH_2$	$Bu^t{\cdot}CH{:}CH_2$	$Bu^t{\cdot}CH_2{\cdot}CH{:}CH_2$
$10^{-3}k_2$	1·05	0·70	0·10

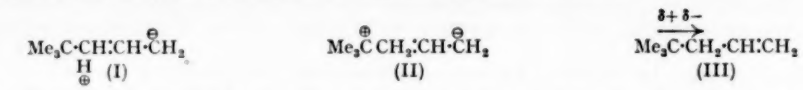
Berliner and Berliner (*J. Amer. Chem. Soc.*, 1950, **72**, 222) have recorded corresponding relative rates for bromination of alkylbenzenes, and have made plausible estimates of the ratios of *ortho*- to *para*-substitution, from which may be derived the following relative rates of *para*-substitution: $PhBu^n$, 1·0; $PhBu^t$, 0·42; $Ph{\cdot}CH_2Bu^t$, 0·35.

Alkyl groups favour electrophilic substitution by an inductive effect ($+I$; $Bu^t > Bu^n >$ Me), and by hyperconjugation ($+T$; $Me > Bu^n > Bu^t$). The decrease in the rate of bromine substitution from toluene to *tert.*-butylbenzene was interpreted by de la Mare and Robertson (*J.*, 1943, 279), and by Berliner and Berliner (*J. Amer. Chem. Soc.*, 1949, **71**, 1195), as a manifestation of decreasing hyperconjugation, for which the increasing inductive effect does not completely compensate. The rates of bromine addition to *n*-butyl- and *tert.*-butyl-ethylene are more nearly equal. This may be explained by the hypothesis that the inductive effect, being electrostatic in origin, is more effective in the ethylenic than in the *para*-position of the aromatic system, since in the former the substituent is nearer to the point of electrophilic attack. Similarly was explained the observation (*J.*, 1950, 1624) that the order of rates for substitution, PhMe > PhEt, becomes reversed with respect to the two alkyl groups for addition, in the example, $CHEt{:}CH{\cdot}CO_2H >$ $CHMe{:}CH{\cdot}CO_2H$.

As electrophilic addition is a two-stage process resulting in *trans*-additon with inversion, there exists the possibility of steric hindrance in the second phase of the reaction. In the case of *tert.*-butylethylene, there is involved a *neo*pentyl-like structure, $Me_3C{\cdot}\overset{\oplus}{C}H{\cdot}CH_2Br$, which should be especially favourable for causing steric hindrance to the approach of the nucleophilic reagent required for completion of the addition. The observed rate of bromination of this compound, however, is as predicted from comparison with *n*-butylethylene, for which steric hindrance would not be expected. Similarly, the results for the *cyclo*alkenes, described later in this communication, and for certain other compounds (cf. *J.*, 1950, 1624), support the conclusion that this type of steric hindrance does not operate, or is of very minor importance, in halogen addition.

The *neo*pentyl group, as indicated by the rates of bromine addition to *neo*pentylethylene and of bromination of *neo*pentylbenzene, is characterised by a low power of electron-release, in comparison with a group such as *n*-butyl. As the inductive effects of such groups would be expected to be similar, the cause of the difference would appear to lie in a variation in the tautomeric effect. The low rates for the *neo*pentyl-substituted compounds are remarkable; it might have been expected, for example, that the facilitation of the reaction by the hyperconjugative structure (I) would be augmented by contribution from structure (II). However, it seems possible that the inductive influence of the *tert.*-butyl group may, by transference of a fractional charge to the adjacent carbon atom, as illustrated in (III), tend to be unfavourable to the development of structure (I), and in this way may reduce the effectiveness of the *neo*pentyl group in promoting reaction by mechanisms favoured by this type of structure. In *neo*pentylbenzene, owing to the relatively greater distribution of charge in the aromatic ring, the effect may be less, as is shown in the smaller

spread of relative rates. In the allyl halides, as is discussed in a later section, the inductive influence of the halogen substituent acts in the opposite direction.



(I) (II) (III)

(b) *Compounds* CHR:CHR'.—The following rates of bromine addition have been measured :

Compound :	Bu^n·CH=CH_2	Me·$[CH_2]_7$·CH=CH_2 / MeO_2C·$[CH_2]_7$·CH=CH_2	$[CH_2]_6$(CH=CH)	$[CH_2]_3$(CH=CH)
$10^{-3}k_2$	1·05	30	30	40

In methyl oleate (*J.*, 1950, 1628), the carboxymethyl group is too far away from the ethylenic system to have an appreciable effect on the rate of reaction, and this compound may therefore be considered analogous to a *cis*-1 : 2-dialkylethylene, in which the second substituent increases the reactivity by a factor of about thirty. The values for *cyclo*pentene and *cyclo*hexene show that cyclic structures have no special influence on the rate of bromine addition. This result would be expected only if the second phase of the reaction were not rate-determining. These compounds, therefore, provide further evidence that steric hindrance of this type is not a controlling factor in halogen addition.

(*c*) *Compounds* CRR':CH_2.—The following are some further comparisons of reactivity :

Compound :	*n*-Bu·CH:CH_2	CMeEt:CH_2	Camphene	CPhMe:CH_2
$10^{-3}k_2$	1·05	30	40	30

An ethyl group does not differ greatly from a *n*-butyl group in its influence on the reactivity, and the methyl group in ethylmethylethylene is seen to increase the rate of bromine addition by a factor of about thirty. The ratio of rates of bromine addition in methylene chloride as solvent, with hydrogen bromide as catalyst, has been recorded by the competition method for the compounds CHMe:CH_2 and CMe_2:CH_2 as 1 : 2 (Ingold and Ingold, *J.*, 1931, 2354). Direct measurements of bromine addition in chloroform solution with M/1000-olefin, M/2000-bromine, and added M/100-hydrogen bromide, at 25°, gave the values for k_2, *n*-Bu·CH:CH_2 20, and CMeEt:CH_2 500. The relative reactivity (ratio of rates, 1 : 29 in acetic acid, 1 : 25 in chloroform with hydrogen bromide as catalyst) is little affected by the change in conditions. This comparison confirms the previous discovery (de la Mare, Scott, and Robertson, *J.*, 1945, 509), that the kinetic rate ratio may in certain cases considerably exceed that found by the competitive method.

Bromine addition to camphene involves molecular rearrangement to form the 1 : 3-dibromo-derivative. Such a change need not necessarily influence the rate of bromine addition, since the rearrangement may occur in a stage of the reaction which is not rate-determining. In fact, camphene reacts at a rate almost the same as that of other hydrocarbons of the type CR_2:CH_2.

A phenylalkylethylene is included for comparison with the dialkylethylenes. The phenyl group, compared with ethyl by reference to such compounds as CHPh:CH·CO_2H and CHEt:CH·CO_2H, increases the rate of bromine addition by a factor of about seven. The relatively small effect of the former group in the comparison of ethylmethylethylene with α-methylstyrene suggests that the phenyl group is prevented by the methyl from rotating into the position most favourable for conjugation with the ethylene link. The ionisation potential of α-methylstyrene, compared with that of styrene, is explained similarly by Walsh (*Ann. Reports*, 1947, **44**, 34).

(d) *Halogenoalkylethylenes.*—In previous papers (*J.*, 1944, 131; 1947, 630; 1950, 812), there has been discussed the unexpected order of reactivity, *viz.*, CH_2Cl·CH:CH_2 > CH_2Br·CH:CH_2, found for third-order bromine addition in acetic acid both with and without added hydrogen bromide ($-d[Br_2]/dt = k[A][Br_2]^2$ or $k[A][Br_2][Br^-]$; products dibromide and bromoacetate *), for halide-ion-catalysed bromine addition ($-d[Br_2]/dt = k[A][Br_2][Cl^-]$; products dibromide and bromochloride *), and for third-order addition in chlorobenzene

* Cf., *e.g.*, Nozaki and Ogg, *J. Amer. Chem. Soc.*, 1942, **64**, 697.

$(-d[Br_2]/dt = k[A][Br_2]^2$; products dibromide). The same order was found for the chlorination of the benzyl halides, *i.e.*, $Ph{\cdot}CH_2Cl > Ph{\cdot}CH_2Br$. We consider, therefore, that the sequence $CH_2Cl > CH_2Br$ represents the true order of effectiveness of these groups in their influence on electrophilic reactions of halogens, in view of the appearance of this order under so many diverse conditions of reaction, solvent, and catalyst. It was nevertheless considered of interest to extend the series to include allyl fluoride, and the following are the rates of bromine addition in acetic acid solution at 25° :

	$CH_2F{\cdot}CH{:}CH_2$	$CH_2Cl{\cdot}CH{:}CH_2$	$CH_2Br{\cdot}CH{:}CH_2$
Rate (as k_2, $x = 20$, M/80)	2·9	1·6	1·0

The same order was found in the presence of lithium chloride as catalyst.

Two modes of reaction are possible for these compounds, depending on the two possible positions for electrophilic attack :

The contribution of the second process in the total reaction has been calculated (*J.*, 1950, 814) to be 12%, approximately the same as the value found for *meta*-substitution in benzyl chloride, in which the aromatic ring is affected by similar electronic drifts (cf. Ingold and Shaw, *J.*, 1949, 975). The relative rate order shown above for the allyl halides is therefore chiefly due to the operation of the mechanism (*A*), and the effect of mechanism (*B*) is merely to reduce slightly the spacing of the series.

The allyl halides add bromine considerably less rapidly than does propylene, the rate factor being greater than 10^3, as must be expected in view of the powerful electron-withdrawing influence ($-I$) of halogen substituents. This influence, however, decreases in the order $F > Cl > Br$, and thus, on the basis only of the inductive effect, the reactivities of these compounds would be expected to fall in a sequence opposite to that observed. The electron-donating properties ($+T$) of the halogens ($F > Cl > Br$; cf. de la Mare and Robertson, *J.*, 1948, 100) cannot reasonably be invoked to explain the present results, since in the allyl compounds the halogen substituent is not conjugated with the double linking; nor does carbon–halogen hyperconjugation (cf. de la Mare, Hughes, and Ingold, *J.*, 1948, 17) appear to give a satisfactory explanation, as this effect would here be expected to augment the inductive effect.

It is possible to describe the relative reactivities of these compounds by the postulate that the extent of hyperconjugation from the C–H bonds of a group CH_2X is altered by X in such a way as to give the order of electron release $CH_2F > CH_2Cl > CH_2Br$. It is suggested that the loosening of the carbon–hydrogen electrons required for hyperconjugation is determined by the inductive effect of the group X. A similar order of reactivity for aromatic substitution should be expected for the series $Ph{\cdot}CH_2X$, and has been found for the chloride and bromide.

Finally, reference is made to the compound $(CH_2Cl)_2C{:}CH_2$, as the earlier theoretical explanation (*J.*, 1947, 630) of its behaviour must be modified in the light of later developments. By reference to the reactivities of ethylene and allyl chloride (*J.*, 1950, 812), the following relative rates of bromine addition may be assessed :

$CH_2{:}CH_2$	$CH_2Cl{\cdot}CH{:}CH_2$	$(CH_2Cl)_2{\cdot}C{:}CH_2$
1	0·019	0·00024

The reactivity of the bischloromethyl compound is thus of the expected low order and is not attributable to the influence of steric hindrance. Likewise, the large catalytic influence of lithium chloride on the rate of bromine addition to this compound (reactants M/80, +M/20-lithium chloride, 22-fold acceleration compared with the value of 6·3 for allyl chloride) may be explained without reference to the operation of steric influences. The compound $(CH_2Cl)_2C{:}CH_2$ belongs to the general class of compounds, $CHR{:}CH_2$, containing a group R with a ($+T$, $-I$) characteristic (*J.*, 1949, 298). This classification may be extended

to include compounds of the class $CR_2{:}CH_2$, with two such groups attached to the same carbon atom, for which compounds it is not unreasonable to expect an especially large catalytic effect.

We are indebted to Professor E. D. Hughes, D.Sc., F.R.S., for valuable discussion of this manuscript, and for permission to refer to unpublished measurements on allyl fluoride and *neo*-pentylethylene, made in collaboration with P. B. D. de la Mare, M.Sc., Ph.D., and C. A. Vernon, B.Sc., to whom we are also greatly indebted.

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180. *Hydrated Calcium Silicates. Part III.* Hydrothermal Reactions of Mixtures of Lime : Silica Molar Ratio 3 : 2.*

By L. HELLER and H. F. W. TAYLOR.

Hydrothermal treatment of mixtures of lime and silica gel in the molar ratio 3 : 2 yields calcium silicate hydrate (I) as the sole product at temperatures below 140°. This product gives an *X*-ray pattern almost the same as that of similarly prepared material of lime : silica ratio 1 : 1. At higher temperatures, at least up to 180°, calcium silicate hydrate (I) appears to be the initial product. More prolonged treatment yields at 140—160° afwillite, and at 180—200° principally xonotlite and hillebrandite.

PART II * of this series dealt with reactions of mixtures of lime and silica gel of molar ratio 1 : 1. Similar reactions of mixtures of lime : silica ratio 3 : 2 are now described. The investigation was carried out to study the products obtained below 200°, the maximum temperature commonly employed for the steam curing of Portland cement, and in particular to establish whether calcium silicate hydrate (I) could be formed under hydrothermal conditions from preparations of this composition.

Previous Work.—Three investigations on this range of composition have been reported. Nagai (*Z. anorg. Chem.*, 1932, **206**, 177; **207**, 321) found that hydrothermal treatment for 6 days at 153° of a mixture of lime and quartz yielded a compound which he identified optically as afwillite. Similar experiments at 180° and 200° gave xonotlite mixed with a phase described as needles of composition $3CaO,2SiO_2,H_2O$. The analyses were corrected for the presence of unchanged calcium hydroxide, determined by extraction with glycerol, and of quartz which was regarded as the residue insoluble in aqueous sodium carbonate. Büssem ("Symposium on the Chemistry of Cements," Stockholm, 1938, 141) took *X*-ray photographs of two of Nagai's preparations and affirmed that the products which Nagai had described as afwillite were actually dicalcium silicate α-hydrate.† He claimed that these two compounds were almost indistinguishable by optical methods.

Flint, McMurdie, and Wells (*J. Res. Nat. Bur. Stand.*, 1938, **21**, 617) obtained CaO,SiO_2,H_2O at 150—200° and xonotlite at temperatures up to 400°. They inferred the presence of another phase from the overall composition but failed to observe it experimentally.

Jander and Franke (*Z. anorg. Chem.*, 1941, **247**, 161) carried out experiments at 300° and 350°. They found that the products of short-term hydrothermal treatment at 300° were a mixture of xonotlite and hillebrandite, while longer periods of heating gave in addition a compound described as $3CaO,2SiO_2,H_2O$. Taylor and Bessey (*Mag. Concrete Res.*, 1950, **4**, 15) suggested that this may have been foshagite. At 350° only the $3CaO,2SiO_2.H_2O$ was produced.

The earlier investigators thus agree in finding xonotlite as one of the products at 180° or above. Otherwise there is little agreement, especially regarding the lower-temperature products. In no case was the formation of calcium silicate hydrate (I) observed.

* Part II, *J.*, 1951, 2397.

† The nomenclature used for the dicalcium silicate hydrates is that of Bessey (*op. cit.*, p. 178).

Experimental.—The experimental methods, and the samples of calcium hydroxide and silica gel used as starting materials, were identical with those described in Part II (*loc. cit.*). The calcium hydroxide contained, as the only significant impurities, CO_2, 0·65; Na_2O, 0·11%.

For the purpose of comparison, *X*-ray powder photographs were taken of natural xonotlite, afwillite, and hillebrandite. The results were in satisfactory agreement with those recorded in the literature (see Taylor and Bessey, *loc. cit.*).

The conditions of each experiment, and the products as identified by optical and *X*-ray methods, are given in Table 1.

TABLE 1. *Products of hydrothermal reactions.*

Exp. No.	Temp.	Duration (days)	Products *
90	110°	42	CSH(I) ‖
56	130	56	CSH(I) ‖
57	130	60	CSH(I) ‖
65	140	90	CSH(I) ‖ + AFW
73	140	120	CSH(I) ‖ + AFW
74	140	54	CSH(I) ‖ + AFW
48	150	40	CSH(I) ‖
19	160	5	CSH(I) + little CC
22	160	15	CSH(I) + AFW
83	180	2	CSH(I) + CC + SiO_2 gel + CH
94	180	14	XON + β + α
95	180	30	β + possible γ
25	200	20	β + XON + α
26	200	22	β + XON + α

* CSH(I) = Calcium silicate hydrate (I); ‖, in a well crystallised form, see text; AFW = afwillite; CC = calcium carbonate; CH = calcium hydroxide; XON = xonotlite; α, β, γ = dicalcium silicate α-, β-, and γ-hydrates, respectively.

DISCUSSION

Calcium Silicate Hydrate (I).—At temperatures up to about 130° (Expts. 90, 56, and 57) this was the sole product detectable by *X*-ray or optical methods. At higher temperatures, it was formed alone only after short periods of treatment (Expts. 19 and 83). More prolonged treatment yielded additional or alternative products. Calcium silicate hydrate (I) thus appears, as in the case of mixtures of lime : silica ratio 1 : 1, to be a transition product at the higher temperatures.

The poorly crystallised material obtained in Expts. 19 and 83 yielded *X*-ray patterns identical with those of samples having a lime : silica ratio 1 : 1 and showing a similar degree of crystallisation. The better crystallised material obtained in Expts. 90, 56, etc., gave photographs almost identical with those of the correspondingly crystallised samples of lime : silica ratio 1 : 1. A few minor differences were observed in the *X*-ray patterns of these samples; lines showing variations in spacing or intensity are given in Table 2. In all other respects the *X*-ray patterns were the same as that of sample 58, described in the previous paper.

Only in the case of sample 83 could unchanged calcium hydroxide be detected in the products. The invariability of the *X*-ray pattern of calcium silicate hydrate (I) with lime : silica ratio, has already been demonstrated as regards the limited number of spacings shown by the room-temperature preparations (Part I, *J.*, 1950, 3682). The present results show that this extends at least approximately to the fuller patterns given by the more crystalline materials. The explanation of this effect is still not clear.

TABLE 2. *Variations in the* X*-ray powder patterns of calcium silicate hydrate* (I) ‖ *samples.*

Line (Å)	Intensity in different samples: 58	56	57	65	74	48
2·48	w	w	absent	w	absent	w
2·28	ms	ms	mw/d	vvw	absent	absent
2·22	vw	vw	absent	vvw	absent	ms
2·07	ms	ms	mw	mw	mw	m
1·88	vw	vw	vw	w	vw	split into doublet

The significance of this table lies in the comparison of the relative intensities of the lines from sample to sample; *e.g.*, the 2·28 and 2·07 Å lines are of the same intensity in samples 58, 56, and 57, but not in samples 65, 74, and 48.

Afwillite.—This was identified optically and by *X*-ray methods. Samples 65, 73, 74, and 22 gave *X*-ray powder patterns identical with those of the natural mineral mixed with calcium silicate hydrate (I). Moreover, a single crystal was selected from sample 22, and oscillation photographs taken about two crystallographic axes; the axial lengths so determined agreed closely with those found by Megaw for natural afwillite. The photographs could be indexed satisfactorily on the basis of Megaw's unit cell ($a = 16{\cdot}27$, $b = 5{\cdot}63$, $c = 13{\cdot}23$ Å, $\beta = 134° 48'$; private communication).

The present results indicate that afwillite is probably the final product of the hydrothermal reactions at 140—160°. However, the presence of a considerable amount of calcium silicate hydrate (I) in samples which had reacted for as long as four months suggests that the reaction would require very prolonged treatment for its completion.

Nagai's original characterisation of the product which he obtained at 153° as afwillite is in agreement with our results. We cannot confirm Büssem's observation that afwillite is optically very difficult to distinguish from dicalcium silicate α-hydrate. Although the principal refractive indices of the two compounds are very similar, afwillite forms characteristic needles of considerable thickness, unlike any other hydrated calcium silicate, whereas dicalcium silicate α-hydrate, in our experience, occurs as thin plates.

We are unable to correlate our results with those of Flint, McMurdie, and Wells, who failed to find either calcium silicate hydrate (I) or afwillite in any of their products, but recorded the formation of a compound CaO,SiO_2,H_2O, which we have shown to differ from calcium silicate hydrate (I) (Part II, *loc. cit.*). We could not obtain this compound from any mixtures having lime : silica ratios greater than 1 : 1.

Xonotlite and Hillebrandite.—The results of the experiments at 180° and 200° were difficult to interpret but indicated xonotlite and hillebrandite (dicalcium silicate β-hydrate) as the main products. Comparison of the *X*-ray powder photographs with those of the natural minerals showed in sample 94 all the lines of xonotlite together with the strongest lines of hillebrandite. Samples 25 and 26 gave patterns very similar to natural hillebrandite together with the strongest lines of xonotlite. Sample 95 showed hillebrandite and also the strongest line of dicalcium silicate γ-hydrate. In three of the samples a few crystals of dicalcium silicate α-hydrate could also be detected optically and by single crystal *X*-ray photographs. The structure of this compound was investigated and will be discussed elsewhere.

Optical investigation showed all three samples to consist principally of very small acicular crystals (under 10μ long) of positive elongation and refractive index near to 1·59. These data are compatible with either xonotlite or hillebrandite. Further optical data which would have distinguished between them could not be obtained owing to the small size of the crystals. It was thus not possible to confirm the conclusion derived from the *X*-ray data that the relative proportions of the two compounds were not the same in the four samples. The reason for the anomaly is not clear: if xonotlite and hillebrandite are the only products they must be formed in equimolar amounts. A possible explanation is that preferential crystallisation of either compound can occur, the other remaining in a badly crystallised state giving rise to a weak *X*-ray pattern.

These results can be correlated with those of Jander and Franke, who obtained a mixture of xonotlite and hillebrandite at 300°. Nagai, and Flint, McMurdie, and Wells also obtained xonotlite at 180—200° and 250°, respectively, together with other products. The most probable interpretation of the present and earlier results at temperatures of 180° and above is that the main products are xonotlite and a hydrated dicalcium silicate which is usually the β-, but may under certain conditions be the α- or the γ-hydrate.

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181. 22-isoallo*Spirost*-8(14)-*en*-3β-*ol and* 3β-*Hydroxy*allo*pregn*-8(14)-*en*-20-*one*.*

By O. Mancera, D. H. R. Barton, G. Rosenkranz, and Carl Djerassi.

22-*isoallo*Spirost-8(14)-en-3β-yl acetate has been prepared by Raney-nickel-catalysed hydrogenation of the corresponding 5 : 7- and 7 : 9(11)-dienes and also by catalyst-hydrogen-induced double-bond rearrangement of the corresponding Δ^7-compound. The acetate has been characterised by various derivatives and has been converted, *via* the appropriate furosta-8(14) : 20(22)-diene derivative into 20-keto*allo*pregna-8(14) : 16-dien-3β-yl acetate. Hydrogenation of the latter gave 20-keto*allo*pregn-8(14)-en-3β-yl acetate, also prepared by double-bond rearrangement of the corresponding Δ^7-compound.

The 8(14)-olefinic linkages in these compounds are *not* rearranged to the 14(15)-positions by the action of hydrogen chloride.

The molecular rotation data are discussed briefly.

Investigations in the *trans*-A/B stenol series (I; R = alkyl; but with one nuclear double bond) have led to unambiguous characterisation of the possible double-bond positions by both chemical and optical methods (for an excellent summary see Fieser and Fieser, "Natural Products Related to Phenanthrene," Reinhold Publ. Corp., 1949). In compounds of this type R normally contains 8 or more carbon atoms. On the basis of our current theoretical concepts of the relation between chemical reactivity (or thermodynamic stability) and molecular structure it would be expected that changes in the nature of the side chain would not exert major chemical effects at isolated double-bond positions in the nucleus, for example, at positions 7(8), 8(9), or 8(14). So far as molecular rotation relations are concerned it is not possible to make such a precise estimate of the limiting interactions of substituent groups. However by analogy with the work of Barton and Cox (*J.*, 1948, 783) it would be expected that optical interaction of the nuclear double-bond positions with the side chain would not be significant provided (*a*) that the latter was not too unsaturated and (*b*) that it did not exert a distorting effect on the molecular framework. Clearly the definition of these two terms is not precise and their significance, in the absence of an adequate theory of optical activity, can only be assessed by empiricism. Recent advances in the steroidal sapogenin series have now made available substances with double bonds at various positions in the nucleus and having a sapogenin or acetyl side chain attached to ring D. It is with the properties of such compounds that the present communication is concerned.

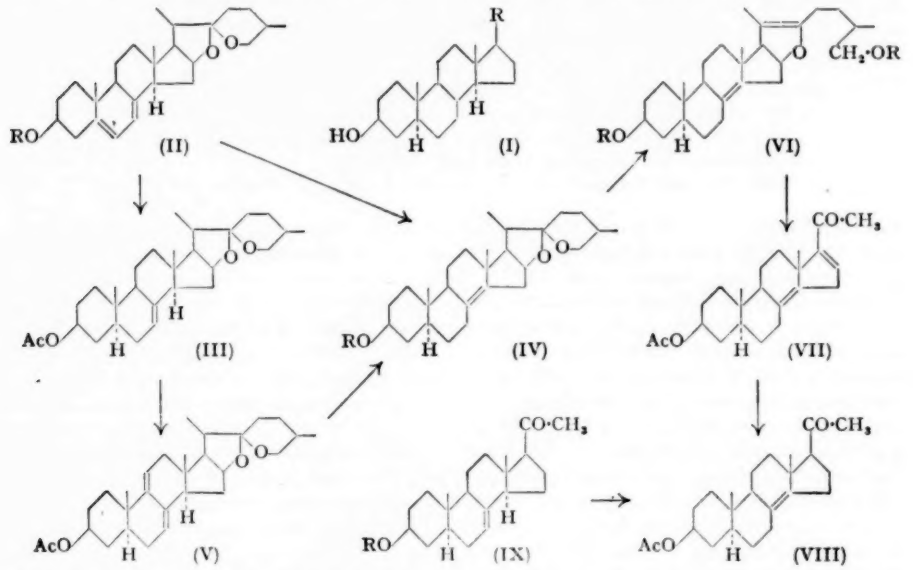
In a recent paper (Rosenkranz, Romo, and Berlin, *J. Org. Chem.*, 1951, **16**, 290) we reported the preparation of 22-*isoallo*spirosta-5 : 7-dien-3β-ol (II; R = H) and derivatives (cf. Chamberlain, Chemerda, Tishler, *et al.*, *J. Amer. Chem. Soc.*, 1951, **73**, 2396). Hydrogenation of the acetate (II; R = Ac) at a platinum catalyst in ethyl acetate solution gave 22-*isoallo*spirost-7-en-3β-yl acetate (III) (Rosenkranz, Romo, Batres, and Djerassi, *J. Org. Chem.*, 1951, **16**, 298). We now find that hydrogenation of (II; R = Ac) at high pressure and high temperature in presence of Raney nickel (cf. Bladon, Fabian, Henbest, Koch, and Wood, *J.*, 1951, 2402) affords 22-*isoallo*spirost-8(14)-en-3β-yl acetate (IV; R = Ac).† The same compound was also obtained by double-bond rearrangement of (III) (*a*) with a palladised charcoal catalyst in ethyl acetate–acetic acid solution and (*b*) under the same Raney nickel hydrogenating conditions. Similar Raney nickel hydrogenation of 22-*isoallo*spirosta-7 : 9(11)-dien-3β-yl acetate (V), prepared (Rosenkranz, Romo, Batres, and Djerassi, *loc. cit.*) by mercuric acetate dehydrogenation of (III), likewise afforded (IV;

* This paper is Part XVII in the Syntex series on Steroidal Sapogenins; for Part XVI see Djerassi, Batres, Velesco, and Rosenkranz, *J. Amer. Chem. Soc.*, in the press. It is also to be regarded as Part XVIII in the series (by D. H. R. B.) on "The Application of the Method of Molecular Rotation Differences to Steroids"; for Part XVII see Barton and Rosenfelder, *J.*, 1951, 2381.

† The compound to which this constitution was previously assigned (Rosenkranz, Romo, Batres, and Djerassi, *loc. cit.*) has been shown to be a mixture of the 8(14)- and 7(8)-unsaturated isomers, rearrangement of the latter to the former having been incomplete owing to the use of too little acetic acid in the hydrogenation medium.

R = Ac). Alkaline hydrolysis of 22-*isoallo*spirost-8(14)-en-3β-yl acetate afforded the corresponding alcohol (IV; R = H) further characterised as the benzoate. The homogeneity of these compounds was carefully established by methods summarised in the Experimental section.

The assignment of the ethylenic linkage to the 8(14)-position in these compounds is based on the following evidence: first, analogy to reactions already well established in the stenol series (Fieser and Fieser, *op. cit.*); secondly, the molecular-rotation differences on acylation (see discussion below); thirdly, the ultra-violet spectra (see Experimental)



which indicate a tetrasubstituted double bond exocyclic to two rings rather than a tetrasubstituted double bond of the 8(9)-stenol type (see Bladon, Henbest, and Woods, *Chem. and Ind.*, 1951, 866; Halsall, *ibid.*, p. 867); fourthly, the acetate failed to react with osmium tetroxide in ethereal solution. Ergost-8(14)-en-3β-yl acetate is likewise unaffected by this reagent whereas the corresponding 8(9)-isomer reacts readily (see Barton and Cox, *J.*, 1949, 214).

On treatment with acetic anhydride at 200° 22-*isoallo*spirost-8(14)-en-3β-yl acetate (IV; R = Ac) was converted into *allo*furosta-8(14) : 20(22)-diene-3β : 26-diol diacetate (VI; R = Ac), characterised by alkaline hydrolysis to the corresponding diol (VI; R = H). Oxidation of (VI; R = Ac) with chromic acid followed by controlled hydrolysis (see Djerassi, Romo, and Rosenkranz, *J. Org. Chem.*, 1951, **16**, 754) afforded 20-keto*allo*pregna-8(14) : 16-dien-3β-yl acetate (VII), hydrogenation of which, at a palladised charcoal catalyst in ethyl acetate solution, gave 20-keto*allo*pregn-8(14)-en-3β-yl acetate (VIII). The acetate (VIII) was also prepared by double-bond rearrangement of 20-keto*allo*pregn-7-en-3β-yl acetate (IX; R = Ac) (Djerassi, Romo, and Rosenkranz, *loc. cit.*) at palladised charcoal in acetic acid. The assignment of the 8(14)-double bond position in the 20-keto-*allo*pregn-8(14)-en-3β-yl acetate is confirmed by its ultra-violet absorption spectrum (see Experimental).

As has long been established, dry hydrogen chloride in chloroform isomerises the 8(14)-double bond in *trans*-A/B-stenols to an equilibrium (cf. Barton, Cox, and Holness, *J.*, 1949, 1771) mixture containing about 50% each of the 8(14)- and the 14(15)-isomer. We found that treatment of 22-*isoallo*spirost-8(14)-en-3β-yl benzoate or acetate (IV; R = Bz or Ac, respectively) under these conditions caused *no* detectable isomerisation of the double bond. A similar observation was made with 20-keto*allo*pregn-8(14)-en-3β-yl acetate (VIII). These

facts show that the nature of the side chain and of its attachment to ring D exerts an influence on the 8(14)- and 14(15)-positions, either in altering the relative stabilities of the two ethylenic linkages (thermodynamic explanation) or (as is less likely) in preventing carbonium-ion formation (kinetic explanation). In either case these observations are contrary to the simple chemical theory outlined in the introductory paragraph. Incidentally they make it probable that the anhydrocorticosterone acetate, m. p. 143°, $[\alpha]_D$ +98°, prepared by Shoppee and Reichstein (*Helv. Chim. Acta*, 1943, **26**, 1316) must have the isolated ethylenic linkage at the 8(14)- rather than at the 14(15)-position (cf. Fieser and Fieser, *op. cit.*, p. 409).

The molecular-rotation data for compounds of the sapogenin series possessing isolated double bonds in the nucleus appear worthy of brief comment. Tables 1 and 2 summarise the molecular rotations of compounds having isolated double bonds at position 5(6), 7(8), or 8(14). In each case (see Table 1) the shift in molecular rotation (Rule of Shift) observed

TABLE 1.

Compound	Molecular rotations: Alcohol	Acetate	Benzoate	Δ_1	Δ_2	Refs.
22-*isoallo*Spirost-5-en-3β-ol	−534°	−578°	−472°	−44°	+62°	(1)
Cholest-5-en-3β-ol	−154	−188	− 74	−34	+80	(2)
22-*isoallo*Spirost-7-en-3β-ol	−315	−306	−295	+ 9	+20	(3)
Ergost-7-en-3β-ol	− 8	− 18	+ 10	−10	+18	(2)
22-*isoallo*Spirost-8(14)-en-3β-ol...	− 99	−146	−140	−47	−41	(4)
Ergost-8(14)-en-3β-ol	+ 44	+ 4	± 0	−40	−44	(2)

Refs. (1) Rosenkranz, Romo, and Berlin, *J. Org. Chem.*, 1951, **16**, 290. (2) Barton and Cox, *J.*, 1948, 783. (3) Rosenkranz, Romo, Batres, and Djerassi, *J. Org. Chem.*, 1951, **16**, 298. (4) This paper.

on acetylation and benzoylation is in good agreement with standard values obtained in the stenol series. When, however, comparisons of the contributions of the ethylenic linkages to the molecular rotations are made (see Table 2) the position is different. Double bonds at 5(6) and at 7(8) in the 22-*isoallo*spirostan-3β-ol nucleus make contributions which are in

TABLE 2. *Contribution of the double bond to the molecular rotation.**

Compound	Sapogenin series, etc.	Stenol series (standard values)	References.
22-*isoallo*Spirost-5-en-3β-ol (diosgenin)	−230°	−253°	(1), (2)
22-*isoallo*Spirost-7-en-3β-ol	− 11	− 68	(3), (4)
22-*isoallo*Spirost-8(14)-en-3β-ol	+205	− 16	(4), (5)
20-Keto*allo*pregn-8(14)-en-3β-yl acetate	+ 45		(2), (5)

* With respect to the corresponding saturated 5-*allo*-compound. For the molecular rotation (−304°) of 22-*isoallo*spirostan-3β-ol (tigogenin) see Ref. (1) in Table 1.

Refs. (1) See Ref. (1), Table 1. (2) See Ref. (2), Table 1. (3) See Ref. (3), Table 1. (4) Barton and Klyne, *Chem. and Ind.*, 1948, 755. (5) This paper.

fair agreement with the standard values of the stenol series. The 22-*isoallo*spirost-8(14)-en-3β-ol described in the present paper is an outstanding exception and demonstrates a strong vicinal effect of the sapogenin side chain, presumably produced by the mutual distorting interactions of the latter with the 8(14)-double bond. This effect is parallel to the anomalous chemical behaviour mentioned above. However 20-keto*allo*pregn-8(14)-en-3β-yl acetate, which shows similar anomalous chemical behaviour, has a molecular rotation contribution for its ethylenic linkage which is in fair agreement with the standard value.

EXPERIMENTAL

M. p.s are uncorrected. All rotations were taken in chloroform solution; the values recorded have been approximated to the nearest degree. Ultra-violet absorption spectra were determined in absolute ethanol solution, with a Unicam Spectrophotometer, Model SP 500. They have not been corrected for instrument error in the 195—220-mμ range (see Bladon, Henbest, and Wood, *loc. cit.*). Infra-red spectra were determined by Srta. Paquita Revaque and her staff for carbon disulphide solutions, with a Perkin–Elmer single-beam model 12-C spectrometer (sodium chloride prism).

Light petroleum refers throughout to the fraction of b. p. 40—60°.

Microanalyses are by Srta. Amparo Barba of the Syntex Microanalytical Dept.

Savory and Moore's alumina for chromatography was used unless stated to the contrary.

22-isoallo*Spirost*-8(14)-*en*-3β-*yl Acetate*.—(a) *By Raney nickel hydrogenation of* 22-iso*spirosta*-5 : 7-*dien*-3β-*yl acetate*. A mixture of spectroscopically pure 22-*iso*spirosta-5 : 7-dien-3β-yl acetate (5·0 g.) (Rosenkranz, Romo, and Berlin, *J. Org. Chem.*, 1951, **16**, 290), W-4 Raney nickel catalyst (3·0 g.) (Pavlic and Adkins, *J. Amer. Chem. Soc.*, 1946, **68**, 1471), and 95% ethanol (200 ml.) was shaken for 8 hours in an autoclave with hydrogen at 1000—1200 lb./sq. in. and 150°. The catalyst was filtered off and extracted well with chloroform, and the combined extract and filtrate were evaporated to dryness. The greenish residue was taken up in chloroform, washed well with dilute acid and water, dried, and evaporated. Recrystallisation from chloroform–methanol yielded 2·9 g. (58%) of colourless crystals with m. p. 200—204°, $[\alpha]_D$ −31·5° (*c*, 0·67), which gave a yellow colour with tetranitromethane, but showed no selective absorption in the ultra-violet above 220 mμ.

Although further crystallisation did not alter the physical properties reported above, a further purification was effected by chromatography. The acetate (3·0 g.) was carefully chromatographed (10 fractions) over alumina. Elution with 1 : 1-benzene–light petroleum afforded pure 22-isoallo*spirost*-8(14)-*en*-3β-*yl acetate* which, recrystallised from chloroform–methanol, had m. p. 210—212°, $[\alpha]_D$ −32° (*c*, 8·11), $[M]_D$ −146°, $\lambda_{max.}$ 203 mμ, $\varepsilon_{max.}$ 7700, ε_{215} 4050 (*c*, 0·0050) (Found: C, 75·9; H, 9·6. $C_{29}H_{44}O_4$ requires C, 76·25; H, 9·7%). The constants were unchanged on repeated recrystallisation.

Under the same conditions of catalytic hydrogenation 22-*iso*spirost-5-en-3β-yl acetate (diosgenin acetate) gave 22-*isoallo*spirostan-3β-yl acetate in 90% yield.

(b) *By Raney nickel hydrogenation of* 22-isoallo*spirosta*-7 : 9(11)-*dien*-3β-*yl acetate*. Similar hydrogenation of 22-*isoallo*spirosta-7 : 9(11)-dien-3β-yl acetate (1·5 g.) (Rosenkranz, Romo, Batres, and Djerassi, *J. Org. Chem.*, 1951, **16**, 298) at W-4 Raney nickel (2·0 g.) in 95% ethanol (80 ml.), afforded the same 22-*isoallo*spirost-8(14)-en-3β-yl acetate (0·31 g.), the identity being confirmed by the infra-red absorption spectrum.

(c) *By rearrangement of* 22-isoallo*spirost*-7-*en*-3β-*yl acetate*. A mixture of 10% palladized charcoal (200 mg.; American Platinum Works, Newark, N.J.), acetic acid (20 ml.), and ethyl acetate (30 ml.) was shaken with hydrogen to pre-reduce the catalyst and then there was added a solution of pure 22-*isoallo*spirost-7-en-3β-yl acetate (2·0 g.) (Rosenkranz, Romo, Batres, and Djerassi, *loc. cit.*) in acetic acid (30 ml.) and ethyl acetate (250 ml.), and shaking under hydrogen was continued for 18 hours (no gas uptake was observed). After working up in the usual way, recrystallisation from chloroform–methanol afforded 22-*isoallo*spirost-8(14)-en-3β-yl acetate (1·72 g.), m. p. 203—206°, $[\alpha]_D$ −35° (*c*, 0·67). The identity was confirmed by the infra-red absorption spectrum.

A similar rearrangement was effected by using W-4 Raney nickel. 22-*isoallo*Spirost-7-en-3β-yl acetate (3 g.) in admixture with the catalyst (3·0 g.) and ethanol (100 ml.) was treated with hydrogen as in the preparation of 22-*isoallo*spirost-8(14)-en-3β-yl acetate reported above. After being worked up in the usual way, the once recrystallised reaction product [1·7 g.; m. p. 197—200, $[\alpha]_D$ −42° (*c*, 0·67)] was chromatographed over 50 g. of alumina (Aluminium Company of America, Alosco grade F-20, minus 80 mesh) and the infra-red spectra of the crystalline eluates were determined. In this way it was shown that 22-*isoallo*spirost-8(14)-3β-yl acetate was eluted first (benzene–hexane = 1 : 4) whilst unchanged starting material was eluted subsequently (benzene–hexane = 2 : 3). Recrystallisation from chloroform–methanol gave 22-*isoallo*spirost-8(14)-en-3β-yl acetate (1·1 g.), m. p. 203—206°, $[\alpha]_D$ −35° (*c*, 0·67), and slightly impure 22-*isoallo*spirost-7-en-3β-yl acetate, m. p. 216—220°, $[\alpha]_D$ −65° (*c*, 0·67), respectively.

22-*isoallo*Spirost-8(14)-en-3β-yl acetate was recovered (75%) unchanged after being shaken with mercuric acetate in chloroform–acetic acid (cf. Rosenkranz, Romo, Batres, and Djerassi, *J. Org. Chem.*, 1951, **16**, 298). It was likewise recovered (78%) when treated with osmium tetroxide in ethereal solution containing a few drops of pyridine for 12 days at room temperature.

Treatment of 22-isoallo*Spirost*-8(4)-*en*-3β-*yl Acetate with Hydrogen Chloride*.—The acetate (800 mg.), prepared by route (a) above, was dissolved in 25 ml. of chloroform and treated with a vigorous stream of hydrogen chloride gas at room temperature for ½ hour. The chloroform was removed *in vacuo* and the residue recrystallised three times from chloroform–methanol, to give pure 22-*isoallo*spirost-8(14)-en-3β-yl acetate, m. p. 210—213°, $[\alpha]_D$ −32° (*c*, 2·95), undepressed in m. p. on admixture with pure acetate [see under (a) above]. Clearly the hydrogen chloride treatment leads to a purification of the acetate, which cannot be effected (see above) by crystallisation alone.

22-isoallo*Spirost*-8(14)-*en*-3β-*yl Benzoate*.—Pure 22-*isoallo*spirosten-3β-yl acetate (750 mg.) (see above) was hydrolysed by 10% potassium hydroxide in boiling 1 : 1 dioxan–methanol (50 ml.) during 2 hours. After being worked up in the usual way, the alcohol was benzoylated (pyridine–benzoyl chloride overnight at room temperature). The *benzoate*, recrystallised twice from chloroform–methanol, had m. p. 179°, $[\alpha]_D$ −27° (*c*, 9·32), −27° (*c*, 8·13), $[M]_D$ −140°, unchanged on further recrystallisation (Found: C, 79·0; H, 9·05. $C_{34}H_{46}O_4$ requires C, 78·7; H, 8·95%).

The benzoate (800 mg.) was treated with dry hydrogen chloride as for the corresponding acetate (see above). One recrystallisation of the product from chloroform–methanol furnished 700 mg. of pure benzoate, $[\alpha]_D$ −27° (*c*, 8·33), m. p. 179°, undepressed on admixture with starting material.

22-isoallo*Spirost*-8(14)-*en*-3β-*ol*.—Pure 22-*isoallo*spirost-8(14)-en-3β-yl benzoate (400 mg.) was hydrolysed with potassium hydroxide in dioxan–methanol as for the hydrolysis of the acetate (see above). The 22-isoallo*spirost*-8(14)-3β-*ol* thus obtained was recrystallised from methanol, and had m. p. 178—179°, $[\alpha]_D$ −24° (*c*, 5·75), $[M]_D$ −99°, giving a marked depression in m. p. on admixture with the starting benzoate (Found: C, 78·05; H, 10·4. $C_{27}H_{42}O_2$ requires C, 78·2; H, 10·2%).

Acetylation (pyridine–acetic anhydride overnight at room temperature) gave back pure 22-*isoallo*spirost-8(14)-3β-yl acetate, thus confirming its homogeneity.

allo*Furosta*-8(14) : 20(22)-*diene*-3β : 26-*diol*.—22-*isoallo*Spirost-8(14)-en-3β-yl acetate (1·0 g.) in acetic anhydride (4 ml.) was heated in a sealed tube at 200° for 10 hours. After the mixture had been poured into water and extracted with ether, the oily furostadienediol diacetate was hydrolysed with 5% methanolic potassium hydroxide (30 minutes' refluxing) and purified by chromatography on 30 g. of ethyl-acetate-washed Alumina (same Alorco grade as above, but left under ethyl acetate for 2 days, filtered, washed with hexane, and reactivated at 100° for 2 days. This type of alumina is neutral and not too active and we have used it for polyhydroxy-adrenal steroids, 17-hydroxy-20-ketones which undergo the D-homo-rearrangement under alkaline conditions, or furosten derivatives). The material eluted with ether was recrystallised twice from hexane–acetone, to give allo*furosta*-8(14) : 20(22)-*diene*-3β : 26-*diol* as rectangular plates, m. p. 167—168°, $[\alpha]_D^{20}$ +54° (*c*, 0·67) (Found: C, 78·1; H, 10·1. $C_{27}H_{42}O_3$ requires C, 78·2; H, 10·2%).

20-*Keto*allo*pregna*-8(14) : 16-*dien*-3β-*yl Acetate*.—22-*isoallo*Spirost-8(14)-en-3β-yl acetate (3·0 g.) was converted into the corresponding furostadiene diacetate as indicated above, and the oily diacetate was oxidised with chromium trioxide and hydrolyzed exactly as described for the corresponding Δ^7-isomer (Djerassi, Romo, and Rosenkranz, *J. Org. Chem.*, 1951, **16**, 754). Recrystallisation from chloroform–methanol yielded 0·85 g. (36%) of colourless 20-*keto*allo*pregna*-8(14) : 16-*diene*-3β-*yl acetate* (Found: C, 77·75; H, 9·05. $C_{23}H_{32}O_3$ requires C, 77·5; H, 9·05%), with the following constants: m. p. 189—190°, $[\alpha]_D$ +90° (*c*, 0·67), infra-red bands at 1760 cm.$^{-1}$ (Δ^{16}-20-ketone), and at 1736 and 1239 cm.$^{-1}$ (acetate bands), in excellent agreement with the values reported by Jones *et al.* (*J. Amer. Chem. Soc.*, 1950, **72**, 956). The ultra-violet maximum at 230 mμ (log ε 4·07) is abnormally low for a Δ^{16}-20-ketone as far as the position of the maximum is concerned, but this has been confirmed a number of times with different batches. Careful chromatography and spectrophotometric analysis of the individual fractions did not give any material with a maximum above 230 mμ. Apparently, this hypsochromic shift is due to the 8(14)-double bond. The only other Δ^{16}-20-ketone with a maximum around 230 mμ is one described by Wagner, Moore, and Folker (*ibid.*, p. 1856).

20-*Keto*allo*pregn*-8(14)-*en*-3β-*yl Acetate*.—(a) *By hydrogenation of* 20-*keto*allo*pregn*-8(14) : 16-*dien*-3β-*yl acetate*. A solution of this acetate (0·5 g.) in ethyl acetate (40 ml.) was shaken with prereduced 10% palladised charcoal (80 mg.) in hydrogen at room temperature and atmospheric pressure. The gas uptake ceased after 20 minutes, 1·1 mols. having been consumed. Recrystallisation from methanol yielded 0·36 g. of 20-*keto*allo*pregn*-8(14)-*en*-3β-*yl acetate* as large prisms, m. p. 154—156°. This material was further purified by chromatography over alumina. The first two fractions eluted with benzene were recrystallised from light petroleum to give the pure acetate, m. p. 156—157°, $[\alpha]_D$ +90° (*c*, 3·41), $[M]_D$ +322°, $\lambda_{max.}$ 205 mμ [$\varepsilon_{max.}$ 10 500, ε_{215} 6700 (*c*, 0·0052)] and 282 mμ (ε 60), infra-red bands at 1706 cm.$^{-1}$ (unconjugated 20-keto-steroid, Jones *et al.*, *loc. cit.*) and at 1736 and 1239 cm.$^{-1}$ (acetate bands) (Found: C, 76·95; H, 9·6. $C_{23}H_{34}O_3$ requires C, 77·05; H, 9·55%).

(b) *By rearrangement of* 20-*keto*allo*pregn*-7-*en*-3β-*yl acetate*. To a prehydrogenated mixture of 10% palladised charcoal (100 mg.), glacial acetic acid (5 ml.), and ethyl acetate (15 ml.) there was added a solution of 20-keto*allo*pregn-7-en-3β-yl acetate (700 mg.) (Djerassi, Romo, and Rosen-

kranz, *loc. cit.*) in ethyl acetate (10 ml.); the mixture was shaken overnight in hydrogen (no gas uptake). After being worked up in the usual way the reaction product was triturated with hexane. Filtration afforded 580 mg. of a colourless solid, m. p. 152—155°, $[\alpha]_D$ +92° (*c*, 0·67). Two recrystallisations from methanol gave pure 20-keto*allo*pregn-8(14)-en-3β-yl acetate, m. p. 155—156°, $[\alpha]_D$ +95° (*c*, 0·67) (Found: C, 76·9; H, 9·5%). The infra-red spectrum was identical with that of a specimen prepared according to (a) above.

Action of Hydrogen Chloride on 20-*Keto*allo*pregn*-8(14)-*en*-3β-*yl Acetate*.—The acetate (200 mg.) in chloroform (10 ml.) was treated with dry hydrogen chloride as detailed above for the 8(14)-sapogenin benzoate. After removal of the chloroform by evaporation *in vacuo*, the product was chromatographed over alumina. Four fractions were collected, each being eluted with benzene (50 ml.) The m. p.s were, respectively, (1) 130—145°, (2) 152—155°, (3) 152—155°, and (4) 140—150°. Recrystallisation of fractions (2) and (3) combined from methanol afforded pure starting material, m. p. 156—157°, $[\alpha]_D$ +89° (*c*, 4·20). Fraction (1), recrystallised, had m. p. 150—152°, fraction (4), m. p. 152—154°. All fractions were undepressed in m. p. on admixture with pure 20-keto*allo*pregn-8(14)-en-3β-yl acetate.

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182. *Polyene Acids. Part IV.* The Three Geometrical Isomers of αα′-Dimethylmuconic Acid.*

By J. A. ELVIDGE, R. P. LINSTEAD, and JOHN F. SMITH.

Methods described in previous papers of this series have been applied to the hitherto unknown αα′-dimethylmuconic acid which has been prepared in all three possible geometrical forms. Peracetic acid oxidation of *p*-xylenol yields the *cis-cis*-isomer (II), m. p. 210°. This is inverted by boiling alkali to the *trans-trans*-acid (VII), m. p. 322°, and isomerised by sulphuric acid to the lactonic acid (III). Treatment of the derived lactonic methyl ester (IV) with sodium methoxide affords a half methyl ester (V), m. p. 115°, of *cis-trans*-αα′-dimethylmuconic acid (VI) which has m. p. 185°. The high-melting *trans-trans*-acid has also been prepared from αα′-dibromo- and αα′-dihydroxy-αα′-dimethyladipic acids, and by hydrolysis of αα′-dimethylmuconononitrile, obtained in poor yield by dehydration of acetonylacetone biscyanohydrin. On catalytic reduction, each of the three stereoisomeric αα′-dimethylmuconic acids affords a mixture of the known *meso*- and racemic forms of αα′-dimethyladipic acid.

αα′-DIMETHYLMUCONIC ACID has not been previously reported in the literature. An examination of scale models indicates that all three of the theoretically possible geometrical isomeric forms (*cis-cis*; *cis-trans*; *trans-trans*) should be capable of existence, as in none of them is there any steric hindrance in the planar *s-trans*-configuration. We have accordingly investigated the acid, partly in extension of the investigation of stereo-isomeric polyene acids reported in earlier papers of this series, and partly as the geometrical forms were of interest for studies of the stereochemistry of hydrogenation. The preparative procedures and the methods for the diagnosis of configuration were extensions of those previously used for the muconic and β-methylmuconic acids (*J.*, 1950, 2235; 1951, 3386).

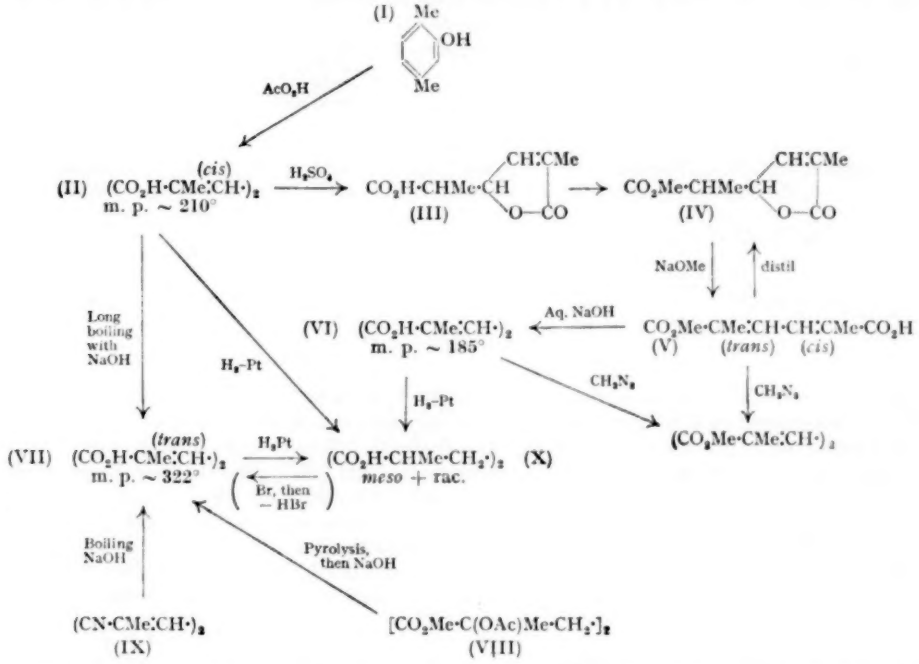
The cis-cis-*Acid*.—Oxidation of *p*-xylenol (I) with peracetic acid gave, in poor yield, αα′-dimethyl-*cis-cis*-muconic acid (II) with m. p. 208—210°, which was converted by diazomethane into the dimethyl ester, m. p. 70°.

The cis-trans-*Acid*.—With cold 80% sulphuric acid αα′-dimethyl-*cis-cis*-muconic acid (II) was isomerised to the unsaturated lactonic acid (III), m. p. 127°, which afforded a liquid methyl ester (IV). Proof of the structure of the lactone is given below. Treatment of this lactonic methyl ester (IV) with methanolic sodium methoxide afforded, as had been expected, an open-chain isomeride, the diene acid ester (V), hydrolysis of which

* Part III, *J.*, 1951, 3398.

provided αα′-dimethyl-*cis-trans*-muconic acid (VI) with m. p. 182—185°. This acid and the half-ester (V) both yielded the same dimethyl ester, m. p. 26—27°, showing that no change of geometrical configuration had occurred during the hydrolysis stage (V) ⟶ (VI). When distilled under reduced pressure, the half-ester (V) readily relactonised to (IV).

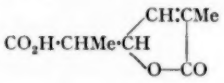
The trans-trans-*Acid.*—Inversion of αα′-dimethyl-*cis-cis*-muconic acid (II) by the prolonged action of boiling sodium hydroxide solution yielded a mixture from which the *trans-trans*-acid (VII), m. p. 320—322°, was separated: its dimethyl ester had m. p. 99—100°. A more satisfactory route to the *trans-trans*-acid (VII) was the vapour-phase pyrolysis at 650° of methyl αα′-diacetoxy-αα′dimethyladipate (VIII), followed by alkaline hydrolysis of the neutral fraction. The diacetoxy-ester (VIII) was prepared from acetonylacetone biscyanohydrin (XIV) as outlined later. Dehydration of this biscyanohydrin afforded in poor yield the diene-dinitrile (IX), alkali hydrolysis of which also provided αα′-dimethyl-*trans-trans*-muconic acid (VII). Less satisfactory was the dehydrobromination with potassium hydroxide of αα′-dibromo-αα′-dimethyladipic ester obtained from mixed *meso*- and racemic αα′-dimethyladipic acids (X): a high-melting product was given which from its properties was essentially αα′-dimethyl-*trans-trans*-muconic acid, but repeated crystallisation failed to raise the melting point above 306—308°.



Configurations.—The configurations of the three acids (II), (VI), and (VII) followed unambiguously from the methods of preparation. The high-melting, sparingly soluble isomer (VII), obtained by elimination processes from disubstituted αα′-dimethyladipic acids, was expected to have an all-*trans*-configuration. This isomer could not be lactonised. The acid (II) obtained by fission of aromatic material was most likely the *cis-cis*-isomer. It lactonised readily to (III). Moreover, it could be isomerised to the high-melting acid (VII) directly and to a third isomer (VI) *via* its lactone (III). Being derived *via* the elimination reaction (IV) ⟶ (V), this third isomeric αα′-dimethylmuconic acid (VI) was expected to have the *cis-trans*-configuration. That the configuration was *cis* about the double bond αβ to the unesterified carboxyl in its half ester (V) was shown by the ready re-lactonisation to (IV).

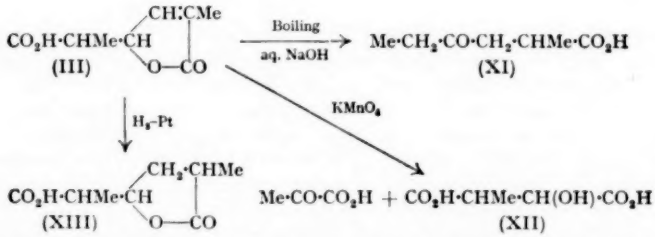
The αγ-diene structures of the αα′-dimethylmuconic acids were confirmed by their behaviour on reduction, and by light-absorption measurements. On catalytic hydrogenation, each of the three acids (II), (VI), and (VII) took up 2 mols. of hydrogen and afforded a mixture of *meso*- and racemic αα′-dimethyladipic acids (X) from which the *meso*-acid was separated in a pure state and compared with authentic material. The ultra-violet light absorption properties of the αα′-dimethylmuconic acids and their methyl esters are recorded in the Table. The shift of the main absorption band to 2800 Å, from 2580 Å in the parent muconic acids (*J.*, 1950, 2235), can be ascribed to hyperconjugation involving the two α-methyl groups. The positions of the main absorption maxima are practically the same for each of the isomeric αα′-dimethylmuconic acids and their esters, whilst there is a small increment in the intensity of absorption for each *cis* ⟶ *trans* inversion. These characteristics, which may be correlated with extended *s-trans*-configurations for all of the geometrical isomers, resemble those of the muconic and β-methylmuconic acids (*J.*, 1950, 2235; 1951, 3386).

Intermediates.—The product, m. p. 127°, of the sulphuric isomerisation of αα′-dimethyl-*cis-cis*-muconic acid was assigned the Δ^{α}-butenolide structure (III) on the following evidence (cf. Elvidge, Linstead, Orkin, Sims, Baer, and Pattison, *J.*, 1950, 2228). The neutralisation and saponification equivalents indicated that the compound was a mono-

Compound		$\lambda_{max.}$ Å	ε	Solvent
$CO_2H{\cdot}CMe{:}CH{\cdot}CH{:}CMe{\cdot}CO_2H$	*cis-cis*	2700	20 400	H_2O
		2810	20 400	
	cis-trans	2690	24 000	EtOH
		2800	25 500	
	trans-trans	2820	31 450	MeOH
$CO_2Me{\cdot}CMe{:}CH{\cdot}CH{:}CMe{\cdot}CO_2Me$	*cis-cis*	2800	24 750	MeOH
	cis-trans	2800	31 600	MeOH
	trans-trans	2820	33 300	MeOH
$CN{\cdot}CMe{:}CH{\cdot}CH{:}CMe{\cdot}CN$		2680	27 700	MeOH
		2760 *	26 400	
		2250	7 100	EtOH

* Inflection.

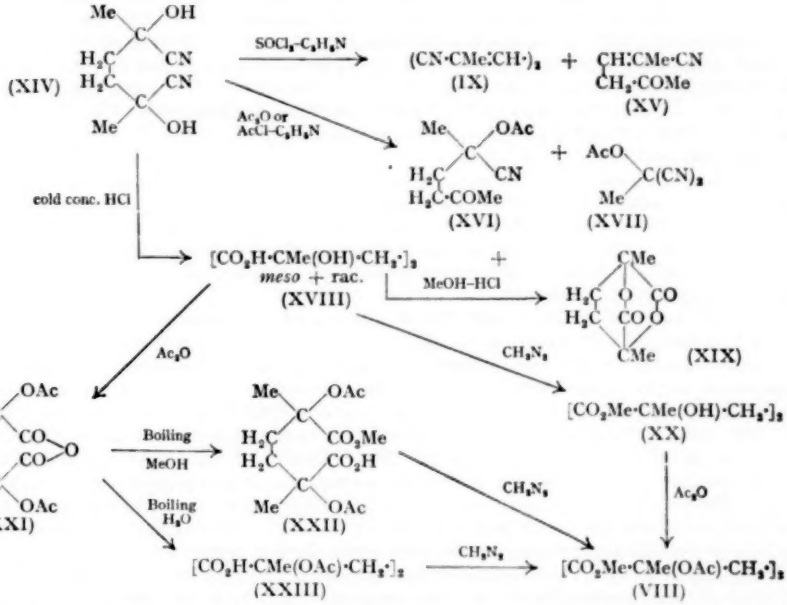
basic lactonic acid. The presence of the 5-membered unsaturated lactone ring was shown by the hydrolysis with boiling alkali to αδ-dimethylævulic acid (XI), isolated as the known semicarbazone. The Δ^{α}-position of the double bond followed from the oxidation with permanganate to pyruvic acid and β-methylmalic acid (XII), which were respectively isolated as the 2 : 4-dinitrophenylhydrazone and bisphenylhydrazide. Confirmation of the Δ^{α}-structure (III) was provided by the light absorption (end absorption only), by esterification with methanolic hydrogen chloride, which proceeded without ring-fission, to give (IV), and by hydrogenation to the saturated lactonic acid (XIII). As expected on the basis of one-sided addition of hydrogen, this reduction product (XIII) seemed to be a single racemate.



Acetonylacetone biscyanohydrin (XIV), utilised for the preparation of (IX) and (VIII), was prepared by the action of liquid hydrogen cyanide on acetonylacetone, and was not

stable enough to be purified by distillation or recrystallisation. The dehydration of the biscyanohydrin to the αα′-dimethylmuconononitrile (IX) was effected with thionyl chloride in dioxan–pyridine. The reaction proceeded in very low yield, much resin was formed, and the dinitrile (IX) was accompanied by a ketonic product. The analysis of the derived 2 : 4-dinitrophenylsemicarbazone indicated that the ketone was C_7H_9ON; and therefore the structure (XV) seems most likely. Treatment of acetonylacetone biscyanohydrin (XIV) with acetic anhydride alone, or with acetyl chloride in pyridine, gave the related acetoxy-ketone (XVI), isolated as the 2 : 4-dinitrophenylhydrazone, together with α-acetoxy-α-methylmalononitrile (XVII), m. p. 67—68°. The last is known to arise from the action of hydrogen cyanide on acetic anhydride (Nef, *Annalen*, 1895, **287**, 265). It is apparent from these results that acetonylacetone biscyanohydrin very readily dismutates with loss of hydrogen cyanide and that the monocyanohydrin thus produced is sufficiently stable to undergo dehydration [to (XV)] and acetylation [to (XVI)].

Hydrolysis of the biscyanohydrin (XIV) with cold concentrated hydrochloric acid proceeded normally to give in moderate yield a mixture of *meso*- and racemic αα′-dihydroxy-αα′-dimethyladipic acids (XVIII) (not separated), together with some of the dilactone (XIX) (Zelinsky and Isajew, *Ber.*, 1896, **29**, 819; Fittig, *Annalen*, 1907, **353**, 1). Attempted esterification of the acids (XVIII) with methanolic hydrogen chloride afforded only the dilactone (XIX), whilst reaction with diazomethane was unsatisfactory in that the acid was sparingly soluble and the necessarily prolonged treatment led to a product difficult to purify. Nevertheless, sufficient methyl αα′-dihydroxy-αα′-dimethyladipate (XX) was obtained for dehydration experiments. The dihydroxy-ester was extremely stable, how-



ever, and could be refluxed unchanged at ordinary pressure and distilled from potassium hydrogen sulphate. No diene ester could be detected after the diol had been heated with phosphoric oxide or with boric acid. Attention was therefore turned to the diacetoxy-derivative (VIII), for which a route alternative to the direct acetylation of the dihydroxy-ester (XX) was desirable.

The mixed αα′-dihydroxy-αα′-dimethyladipic acids (XVIII) were heated with acetic anhydride, and the product subjected to short-path vacuum-distillation. The diacetoxy-anhydride (XXI) was thus obtained in good yield. It reacted only slowly with boiling

methanol to give the half methyl ester (XXII), however, and a better route to the diacetoxy-diester (VIII) than (XXI) $\xrightarrow{MeOH}$ (XXII) $\xrightarrow{CH_2N_2}$ (VIII) was the hydrolysis of the anhydride (XXI) with boiling water to the αα′-diacetoxy-acid (XXIII) followed by esterification with diazomethane. Vapour-phase pyrolysis of the diacetoxy-diester (VIII) thus prepared, followed by hydrolysis of the pyrolysate, then yielded αα′-dimethyl-*trans-trans*-muconic acid, as already mentioned. The mode of formation and stability of the anhydride (XXI) are in agreement with the findings of Adams and Anderson (*J. Amer. Chem. Soc.*, 1951, **73**, 136) who studied the action of acetic anhydride on some ααα′α′-tetramethyl-substituted dibasic acids.

Experimental

αα′-*Dimethyl*-cis-cis-*muconic Acid.*—A solution of *p*-xylenol (90 g.) in 12·7% peracetic acid (1·1 l.) was kept at 0° for several hours, then at room temperature for 7 days. The precipitated αα′-*dimethyl*-cis-cis-*muconic acid* (14 g.) was washed with acetic acid and recrystallised from ethanol; it then had m. p. 208—210° (prismatic needles) (Found: C, 56·7; H, 6·2%; equiv., 85·3. $C_8H_{10}O_4$ requires C, 56·5; H, 5·9%; equiv., 85·1). Similar oxidation of 10 g. of *p*-xylenol afforded only 0·7 g. of diene acid, and from the filtrate, by evaporation under reduced pressure, yellow *p*-xylo-2 : 5-quinone (5 g.) was isolated, m. p. 120—121° (lit., m. p. 125°) (Found: C, 70·7; H, 5·59. Calc. for $C_8H_8O_2$: C, 70·6; H, 5·9%).

Methyl αα′-*dimethyl*-cis-cis-*muconate*, prepared from the foregoing acid by shaking it with ethereal diazomethane, crystallised from aqueous ethanol as laths, m. p. 69—70° (Found: C, 60·3; H, 7·1. $C_{10}H_{14}O_4$ requires C, 60·6; H, 7·1%).

γ-(1-*Carboxyethyl*)-α-*methyl*-Δ^{α}-*butenolide* (2 : 4-*Lactone of* 4-*Hydroxyhex*-2-*ene*-2 : 5-*dicarboxylic Acid*) (III).—(a) *Preparation.* Dimethyl-*cis-cis*-muconic acid (3 g.) was shaken with cold 80% sulphuric acid (30 c.c.), and after 24 hours the solution was poured on ice, and the bulk of the acid neutralised with ammonia. The solution (acid to Congo-red) was extracted with ether overnight, the extract evaporated, and the residue (2·9 g.) crystallised from ether by cooling to −40°. The *lactonic acid* (III) (2 g.) formed long needles, m. p. 126—127°, from water (Found: C, 56·5; H, 6·0%; equiv., 169; hydrolysis equiv., 77·5. $C_8H_{10}O_4$ requires C, 56·5; H, 5·9%; equivs., 170·2, 85·1).

(b) *Action of alkali.* The lactonic acid (III) (0·5 g.) was heated under reflux with aqueous sodium hydroxide (25 c.c.; 10%) for 30 minutes. The solution was cooled, acidified (to Congo-red), treated with semicarbazide hydrochloride (0·8 g.) and saturated aqueous sodium acetate (5 c.c.), and kept overnight. The precipitated semicarbazone of αδ-dimethyl-lævulic acid (0·15 g.) was recrystallised from methanol and had m. p. 157° (lit., m. p. 153°) (Found: N, 21·3. Calc. for $C_8H_{13}O_3N_3$: N, 20·9%).

(c) *Oxidation.* To an ice-cooled, stirred solution of the lactonic acid (III) (1 g.) in water (100 c.c.), potassium permanganate (1·24 g.) in water (200 c.c.) was slowly added. The filtrate from the manganese dioxide was acidified with sulphuric acid and extracted with ether overnight. Evaporation of the extract left an oil, a portion of which with Brady's reagent afforded the 2 : 4-dinitrophenylhydrazone of pyruvic acid (recrystallised from methanol), m. p. and mixed m. p. 213—214°. The remainder of the oil was kept at 80°/15 mm. to remove pyruvic acid, and the residue was then treated with ethereal diazomethane. The solution was evaporated under reduced pressure and the residue heated with an excess of phenylhydrazine under reflux for 3 hours. The excess of the reagent was removed at 120°/15 mm. and the residue triturated with ether to give a white solid, which had m. p. 231—232° (from a bath at 220°) alone and when mixed with β-methylmalic bisphenylhydrazide, and which gave a purple colour when treated in concentrated sulphuric acid solution with ferric chloride (Wislicenus, *Ber.*, 1892, **25**, 196). Authentic β-methylmalic bisphenylhydrazide was prepared similarly from phenylhydrazine and ethyl β-methylmalate. The latter ester (17 g.), b. p. 97°/1 mm., n_D^{26} 1·4321, was obtained by hydrogenation (in ethanol over Adams's catalyst) of 20 g. of ethyl α-oxalopropionate, b. p. 83°/1·5 mm., n_D^{25} 1·4280, prepared from ethyl oxalate and ethyl propionate (*Org. Synth.*, Coll. Vol. II, p. 272).

(d) *Hydrogenation.* Absorption by the lactonic acid (III) (0·5 g.) in methanol (20 c.c.) over Adams's catalyst (100 mg.) was complete in 30 minutes (uptake: 2·4 atoms of H). Filtration and evaporation afforded γ-(1-*carboxyethyl*)-α-*methylbutanolide* (2 : 4-*lactone* of 4-hydroxyhexane-2 : 5-dicarboxylic acid) (XIII), which formed small prisms, m. p. 105—106°, from ether–light petroleum (b. p. 40—60°) (Found: C, 56·15; H, 7·25%; equiv., 179; hydrolysis equiv., 86·5. $C_8H_{12}O_4$ requires C, 55·8; H, 7·0%; equivs., 172·2, 86·1).

(e) *Esterification.* The unsaturated lactonic acid (III) (1·4 g.) was heated with methanol containing 0·3% of hydrogen chloride for 1 hour under reflux, and by distillation, finally at 150—160° (bath-temp.)/20 mm., *γ-(1-carbomethoxyethyl)-α-methyl-*Δ^{α}*-butenolide* (2 : 4-*lactone* of 5-carbomethoxy-4-hydroxyhex-2-ene-2-carboxylic acid) (IV) was obtained: it had n_D^{20} 1·4670, solidified at −40°, and had m. p. *ca.* −20° (Found: C, 58·9; H, 6·8. $C_9H_{12}O_4$ requires C, 58·7; H, 6·5%).

Methyl Hydrogen αα′-Dimethyl-trans-cis-*muconate.*—(a) *Preparation.* To the preceding lactonic ester (IV) (1·3 g.) in methanol (15 c.c.), methanolic sodium methoxide (2·88 c.c.; 2·54N) was added, and after 15 minutes the solution was evaporated under reduced pressure. Water (10 c.c.) was added and the solution at once acidified with hydrochloric acid, whereupon *methyl hydrogen αα′-dimethyl*-trans-cis-*muconate* (0·76 g.) separated: it crystallised from benzene with m. p. 114—115° (Found: C, 58·8; H, 6·7%; equiv., 182; hydrolysis equiv., 90. $C_9H_{12}O_4$ requires C, 58·7; H, 6·5%; equivs., 184·2, 92·1).

(b) *Lactonisation.* When the half ester (0·63 g.) was heated at 160°/18 mm., a liquid distillate (0·57 g.) was collected, which on cooling deposited a few crystals of unchanged starting material, m. p. and mixed m. p. 111—113°. The oil was taken up in ether, the solution washed with aqueous sodium hydrogen carbonate and water, dried (Na_2SO_4), and evaporated, and the residue distilled to yield the Δ^{α}-butenolide (IV) (0·14 g.), n_D^{20} 1·4680.

αα′-Dimethyl-cis-trans-*muconic Acid.*—The lactonic ester (IV) (1·3 g.) was treated with methanolic sodium methoxide as described above, the solution evaporated under reduced pressure, and the crude diene half ester warmed with aqueous sodium hydroxide (10 c.c.; N) on the steam-bath for 1 hour. Acidification of the cooled solution afforded *αα′-dimethyl*-cis-trans-*muconic acid* (0·95 g., 86%), m. p. 175—177°, which after repeated crystallisation from water and from ethanol had m. p. 182—185° (prismatic needles) (Found: C, 56·5; H, 5·9%; equiv., 88. $C_8H_{10}O_4$ requires C, 56·5; H, 5·9%; equiv., 85·1).

Methyl αα′-Dimethyl-cis-trans-*muconate*, b. p. *ca.* 140°/25 mm., m. p. 26—27°, was obtained by shaking the preceding acid with ethereal diazomethane (Found: C, 60·6; H, 7·3. $C_{10}H_{14}O_4$ requires C, 60·6; H, 7·1%). Treatment of methyl hydrogen αα′-dimethyl-*trans-cis*-muconate with ethereal diazomethane, and evaporation of the solution, afforded an identical solid ester.

Acetonylacetone Biscyanohydrin.—(a) *Preparation.* Acetonylacetone (25 g.), containing a few drops of concentrated potassium hydroxide solution, was stirred at 0° for 24 hours with liquid hydrogen cyanide (50 c.c.). Removal of the excess of the latter by passage of nitrogen for 3 hours afforded the biscyanohydrin as a labile solid.

(b) *Dehydration with thionyl chloride.* The biscyanohydrin was dissolved in dry dioxan, pyridine (200 c.c.) was added, and then with ice-cooling and stirring thionyl chloride (60 c.c.) was run in during 4 hours. After a further 4 hours, the cooling-bath was removed, and 24 hours later the mixture was poured into water. On shaking of the mixture with ether, some dark solid separated. The mixture was filtered through kieselguhr and the filtrate extracted with ether. The ethereal layer was separated, washed with dilute sulphuric acid and water, dried (Na_2SO_4), and evaporated. Distillation of the residue at 60—120°/0·5 mm. afforded a mixture of a liquid with some solid (0·8 g.), m. p. 134—138° raised to 141—145° by crystallisation from ethanol. A portion of the solid (100 mg.) in benzene was chromatographed on alumina (10 g.). From the first fractions, *αα′-dimethylmuconononitrile* (IX) was isolated as prisms, m. p. 146—147° (Found: C, 72·7; H, 6·5; N, 20·9. $C_8H_8N_2$ requires C, 72·7; H, 6·1; N, 21·2%). Repeated fractionation of the liquid distillate gave an oil, b. p. 50—56°/0·5 mm., n_D^{21} 1·4578—1·4582, $E_{1\text{ cm.}}^{1\%}$ 100 at 2300 Å., which afforded a 2 : 4-*dinitrophenylsemicarbazone*, m. p. 212—214°, from ethyl acetate (Found: N, 24·5. $C_{14}H_{14}O_5N_6$ requires N, 24·3%).

(c) *Action of acetic anhydride.* The biscyanohydrin from 25 g. of acetonylacetone was heated under reflux with an excess of acetic anhydride for 2 hours, the solution was poured into water, and the mixture warmed to decompose unchanged anhydride. The cooled solution was extracted with ether, and the extract was washed with aqueous sodium carbonate and water, dried (Na_2SO_4), and evaporated. Distillation of the residue at 28 mm. gave two main fractions, b. p. 90—110° and 110—140°. The first fraction solidified, was crystallised from dilute ethanol, and identified as α-acetoxy-α-methylmalononitrile (XVII), m. p. 67—68° (Found: C, 52·0; H, 4·6; N, 19·8. Calc. for $C_6H_6O_2N_2$: C, 52·1; H, 4·4; N, 20·3%). Nef (*loc. cit.*) recorded m. p. 70°. The second fraction had b. p. 167—168°/20 mm. on refractionation, and gave a 2 : 4-*dinitrophenylhydrazone* which crystallised from methanol with m. p. 145·5—146·5° (Found: N, 19·2; 19·5. $C_{15}H_{17}O_8N_5$ requires N, 19·3%).

(d) *Hydrolysis to* (XVIII). The biscyanohydrin from 25 g. of acetonylacetone was stirred with ice-cold concentrated hydrochloric acid (70 c.c.) for 24 hours. The mixture was then

heated on the steam-bath for 2 hours, cooled in ice, and filtered. From water (charcoal), the mixture of *meso*- and racemic αα′-dihydroxy-αα′-dimethyladipic acids (XVIII) separated with m. p. 203—205° (decomp.) (Found: C, 46·4; H, 6·7. Calc. for $C_8H_{14}O_6$: C, 46·6; H, 6·8%). The mother-liquors from the crude acid were evaporated to dryness and the residue extracted with ethanol. Evaporation of the ethanol and crystallisation of the solid from water afforded small prisms of the dilactone (XIX), m. p. 95—96° (Found: C, 56·7; H, 6·1. Calc. for $C_8H_{10}O_4$: C, 56·5; H, 5·9%). Fittig (*loc. cit.*) gives the same m. p. The dilactone (XIX), m. p. 91—92° and mixed m. p. 93—94°, was also obtained when the dihydroxy-dimethyladipic acid (XVIII) was heated under reflux with 5% methanolic hydrogen chloride for 2 hours. After treatment of the dilactone with aqueous sodium hydroxide, or with methanolic sodium methoxide, only αα′-dihydroxy-αα′-dimethyladipic acid was isolated, m. p. and mixed m. p. 203—204° (decomp.).

Methyl αα′-Dihydroxy-αα′-dimethyladipate.—Treatment of the acid (XVIII) with ethereal diazomethane for 2 hours, filtration, and evaporation gave the *methyl* ester (XX) which formed prisms, m. p. 111—112°, from water (Found: C, 51·6; H, 7·8. $C_{10}H_{18}O_6$ requires C, 51·3; H, 7·7%).

Attempts to Dehydrate the Hydroxy-ester (XX).—(i) Methyl αα′-dihydroxy-αα′-dimethyladipate was unchanged (m. p. and mixed m. p.) after being boiled for 5 minutes and then distilled at ordinary pressure. (ii) An intimate mixture of the hydroxy-ester (0·5 g.) and potassium hydrogen sulphate (0·1 g.) was kept at 120° for 30 minutes and at 160° for a further 30 minutes. A solution of the product in water did not rapidly decolorise dilute aqueous potassium permanganate. (The αα′-dimethylmuconic acids are oxidised at once). Neither was any unsaturated material produced by keeping the hydroxy-ester (1 g.) and potassium hydrogen sulphate (1 g.) at 140—150° for 8 hours. (iii) The hydroxy-ester (0·5 g.) and phosphoric oxide (0·5 g.) were heated together at 140° for 15 minutes. The product was treated with ice-water, and the solid crystallised from aqueous ethanol: it had m. p. 105—106° and did not decolorise aqueous potassium permanganate. (iv) After heating of the hydroxy-ester (0·3 g.) with boric acid (0·3 g.) at 130° for 20 minutes no boron-free product could be isolated.

αα′-Diacetoxy-αα′-dimethyladipic Anhydride.—(a) *Preparation.* A solution of the acid (XVIII) in acetic anhydride was heated under reflux for 30 minutes, then evaporated under reduced pressure, and the residue subjected to short-path distillation at 140°/10^{-4} mm. The distillate solidified on trituration with ether and was crystallised from dioxan–ether, to give the *anhydride* (XXI) as prisms, m. p. 163—164° (Found: C, 53·1; H, 6·0. $C_{12}H_{16}O_7$ requires C, 52·9; H, 5·9%).

(b) *Reaction with methanol.* Heating of the anhydride (338 mg.) with methanol under reflux overnight, and evaporation of the solution, yielded methyl hydrogen αα′-diacetoxy-αα′-dimethyladipate (XXII), which separated from aqueous methanol as hexagonal plates of the *monohydrate* (225 mg.), m. p. 95—97° (Found: C, 48·65; H, 6·9. $C_{13}H_{20}O_8,H_2O$ requires C, 48·45; H, 6·8%). After being kept at 60°/0·1 mm. for several hours, the solid anhydrous *half ester* was obtained (Found: C, 51·5; H, 6·7. $C_{13}H_{20}O_8$ requires C, 51·3; H, 6·6%).

(c) *Reaction with water.* The undistilled anhydride from 12 g. of the acid (XVIII) was heated with water until dissolved. On cooling of the solution, *αα′-diacetoxy-αα′-dimethyladipic acid* (XXIII) separated: from aqueous ethanol it formed prisms (13·3 g.), m.p. 207—208° (Found: C, 49·3; H, 6·4%; equiv., 146. $C_{12}H_{18}O_8$ requires C, 49·3; H, 6·2%; equiv., 145·1).

Methyl αα′-Diacetoxy-αα′-dimethyladipate.—(i) Treatment of the preceding acid (XXIII) (13·3 g.) with an excess of ethereal diazomethane and evaporation of the solution yielded the *methyl* ester (VIII) (13·6 g.) which was crystallised from methanol and then benzene, to give square plates, m. p. 163—164° (Found: C, 52·9; H, 7·1%; hydrolysis equiv., 80·6. $C_{14}H_{22}O_8$ requires C, 52·8; H, 6·9%; equiv., 79·6). (ii) An identical ester (2·6 g.) (mixed m. p.) was obtained by heating methyl αα′-dihydroxy-αα′-dimethyladipate (XX) (3·1 g.) with an excess of acetic anhydride for 2 hours, evaporating the solution, and crystallising the residue from ethanol. (iii) The dimethyl ester, m. p. 158—160°, was also obtained from methyl hydrogen αα′-diacetoxy-αα′-dimethyladipate (XXII) and ethereal diazomethane.

αα′-Dimethyl-trans-trans-*muconic Acid.*—(a) *Inversion of the* cis-cis-*acid.* αα′-Dimethyl-*cis-cis*-muconic acid (0·5 g.) was heated under reflux with 20% aqueous sodium hydroxide for 7 hours. The solution was cooled and acidified with dilute sulphuric acid, and the precipitate crystallised from methanol, to yield small prisms of *αα′-dimethyl*-trans-trans-*muconic acid* (50 mg.), m. p. 320—322° (Found: C, 57·2; H, 6·9. $C_8H_{10}O_4$ requires C, 57·0; H, 7·1%).

(b) *By pyrolysis of methyl αα′-diacetoxy-αα′-dimethyladipate.* A stream of nitrogen was passed through the acetoxy-ester (VIII) (7·5 g.) heated at 260—280°, and the issuing vapours were led through a glass tube at 650°, packed with broken glass. The pyrolysate (2·8 g.) was taken up in ether, and the solution washed with aqueous sodium hydrogen carbonate and water,

dried (Na_2SO_4), and evaporated. The residue was warmed with an excess of 2N-sodium hydroxide for 2 hours and the solution acidified. From methanol, the αα′-dimethyl-*trans-trans*-muconic acid (0·52 g.) crystallised with m. p. and mixed m. p. 320—322°.

(c) *From the dinitrile* (IX). αα′-Dimethylmuconitrile (0·6 g.) was heated under reflux with 10% aqueous sodium hydroxide until evolution of ammonia ceased. The solution was cooled and acidified, and the precipitate crystallised from methanol. The product (230 mg.) had m. p. 316—318° alone, and 319—320° when mixed with αα′-dimethyl-*trans-trans*-muconic acid.

(d) *By dehydrobromination of αα′-dibromo-αα′-dimethyladipic acid.* αα′-Dimethyladipic acid (Lean, *J.*, 1894, **65**, 99; Noyes and Kyriakides, *J. Amer. Chem. Soc.*, 1910, **32**, 1057) (18 g.) and thionyl chloride (30 g.) were heated together at 40° until evolution of gases ceased. Excess of thionyl chloride was distilled off, iodine (0·05 g.) was added, and bromine (36 g.) run in slowly with stirring whilst the mixture was heated on the steam-bath and illuminated by means of a 100-watt lamp. Next day, the reaction mixture was poured cautiously into ethanol at 0°, and the resulting solution into an excess of water. The oily ethyl αα′-dibromo-αα′-dimethyladipate (24 g.), isolated by extraction with chloroform, was added slowly to a boiling solution of potassium hydroxide (40 g.) in methanol (100 c.c.) and, after 30 minutes, the solid was collected, washed with methanol, and well drained. A solution of the solid in water was stirred with charcoal, filtered, and acidified with concentrated hydrochloric acid, whereupon crude αα′-dimethyl-*trans-trans*-muconic acid was precipitated (1 g.), m. p. 295—300° not raised above 305—307° on repeated crystallisation from water (Found: equiv., 85·3. Calc. for $C_8H_{10}O_4$: equiv., 85·1).

Attempted Lactonisation of the trans-trans-*Acid.*—αα′-Dimethyl-*trans-trans*-muconic acid (46 mg.) was kept with concentrated sulphuric acid for 24 hours and the solution then poured on crushed ice. The *trans-trans*-acid was precipitated, m. p. and mixed m. p. 320—322° (yield, quantitative.)

Methyl αα′-Dimethyl-trans-trans-*muconate.*—By shaking of αα′-dimethyl-*trans-trans*-muconic acid (100 mg.) with ethereal diazomethane until dissolved, and evaporation of the solution, *methyl αα′-dimethyl*-trans-trans-*muconate* (105 mg.) was obtained, with m. p. 99—100° after being crystallised from aqueous methanol (Found: C, 60·6; H, 7·1. $C_{10}H_{14}O_4$ requires C, 60·6; H, 7·1%).

Hydrogenation of the Isomeric αα′-Dimethylmuconic Acids.—(i) αα′-Dimethyl-*cis-cis*-muconic acid (500 mg.) in methanol (50 c.c.) was hydrogenated in the presence of Adams's catalyst (*ca.* 0·1 g.) (hydrogen uptake: 2·25 mols.). The catalyst was filtered off and the solution evaporated to dryness to yield a mixture of *meso*- and racemic αα′-dimethyladipic acids, m. p. 90—97° (no reaction with aqueous alkaline permanganate), which was stirred with boiling benzene. The insoluble portion crystallised from water and had m. p. 137—138° alone and when mixed with authentic *meso*-αα′-dimethyladipic acid of m. p. 141—143°. (ii) Similarly, after hydrogenation of αα′-dimethyl-*cis-trans*-muconic acid (265 mg.) in methanol over Adams's catalyst (hydrogen uptake: 1·95 mols.), *meso*-αα′-dimethyladipic acid was isolated, having m. p. and mixed m. p. 135—137°. (iii) Hydrogenation of the *trans-trans*-acid proceeded analogously to yield a mixture from which *mezo*-αα′-dimethyladipic acid was isolated.

Analyses were carried out in the microanalytical laboratory (Mr. F. H. Oliver), and measurements of light absorption in the spectrographic laboratory (Mrs. A. I. Boston) of this Department. Grateful acknowledgment is made to the Ministry of Education for a grant (to J. F. S.).

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183. *The Nucleic Acid of Normal and Tumour Tissues. Part II.* The Preparation and Composition of Pentosenucleic Acids from the Fowl Sarcomata, Rous No. 1 and Duran-Reynals "D."*

By R. N. Beale, R. J. C. Harris, and E. M. F. Roe.

Pentosenucleic acids have been prepared from acetone-dried Rous No. 1 and Duran-Reynals "D" fowl sarcomata. The component pentose nucleosides of each have been isolated after quantitative separation by partition chromatography on a starch column (see Part I *). The pentosides of adenine, guanine, cytosine, and uracil alone have been demonstrated. The molar proportions of these are different in each nucleic acid and from the proportions found for G.R.C.H. 15 fowl sarcoma pentosenucleic acid. The overall ratio of purine- to pyrimidine-pentosides shows only slight variation (G.R.C.H. 15, 1·5; Rous No. 1, 1·66; Duran-Reynals "D," 1·41), and the degree of enzymic degradation by ribonuclease is the same for each.

Part I * described the preparation and properties of the pentosenucleic acid from the non-filterable carcinogen-induced fowl sarcoma, G.R.C.H. 15. The investigation of tumour nucleic acids is now extended to the pentosenucleic acids from the virus-induced fowl sarcomata Rous No. 1 and Duran-Reynals "D."

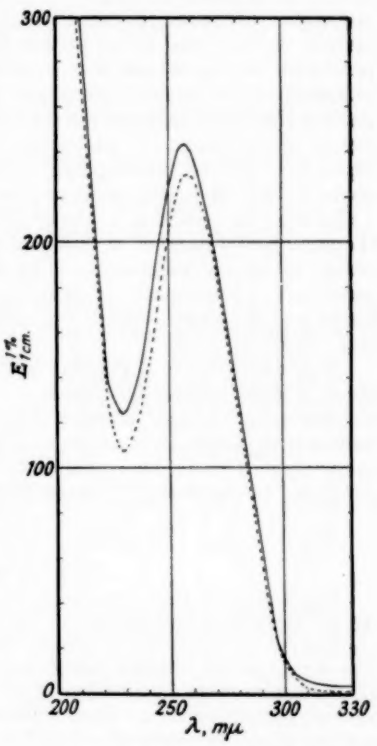
Since 1950 a number of other investigators have prepared "ribonucleic acids" from a variety of sources and analysed them by hydrolysis and separation of the component bases or nucleotides by chromatography on paper or by ion-exchange procedures. It is apparent that, in general, the estimation of the purine moieties is a simple matter and the figures obtained, by either of the above methods, or by differential spectrophotometry, are in good agreement. Greater discrepancies, however, appear in the determinations of uracil and cytosine. For instance, by paper chromatography of the bases Chargaff, Vischer, Doniger, Green, and Misani (*J. Biol. Chem.*, 1949, **177**, 405) found, for pig pancreas pentosenucleic acid, a molar ratio of cytosine to uracil of 4·5, whereas alkaline hydrolysis of the nucleic acid, followed by paper chromatography of the nucleotides, gave a cytidylic acid to uridylic acid ratio of 2·13 (Chargaff, Magasanike, Vischer, Green, Doniger, and Elson, *ibid.*, 1950, **186**, 51). In each case the molar ratio of purine to pyrimidine was 2·25. It is probable therefore that, as a result of alkaline hydrolysis, some 20% of the cytidylic acid had been deaminated to uridylic acid. This suggestion is supported by the observations of Marrian, Spicer, Earl Balis, and Brown (*ibid.*, 1951, **189**, 533), who found that hydrolysis of pentosenucleic acids at room temperature by concentrations of sodium hydroxide greater than N (0·3N at 37°) leads to extensive deamination of cytidylic acid. The common hydrolytic procedure using 0·2N-barium hydroxide at 100° gave 50—100% deamination in 2 hours. Allowance should possibly be made for this effect in the pyrimidine analyses given by Volkin and Carter (*J. Amer. Chem. Soc.*, 1951, **73**, 1516), who effected hydrolysis by 0·5N-sodium hydroxide at 37° for 17 hours, or in those of Marshak (*J. Biol. Chem.*, 1951, **189**, 607) who, before separation and determination of the bases, separated the pentosenucleic from deoxypentosenucleic acid by treatment of the mixture with N-potassium hydroxide at 30° overnight.

Preparation of Pentosenucleic Acid from Rous No. 1 and from Duran-Reynals "D" Sarcoma.—These nucleic acids were prepared by a procedure similar to that already described (*J.*, 1950, 1397) for the pentosenucleic acid from G.R.C.H. 15 sarcoma. However, both tumours contain a mucoid substance which accompanies the pentosenucleic acid during separation from tissue proteins. This mucoid substance was found to be a substrate for hyaluronidase and was accordingly hydrolysed by preliminary treatment of the tissue with this enzyme. The nucleic acids were then extracted with 2% aqueous phenol instead of with physiological saline, and protein contaminants were removed by tryptic digestion in the usual way. Yields of pentosenucleic acid from both sarcomata were similar to

* Part I, *J.*, 1950, 1397.

those obtained from G.R.C.H. 15. The ultra-violet absorption spectra are shown in the figure.

Action of Ribonuclease.—Volkin and Carter (*loc. cit.*) showed that those mammalian pentosenucleic acids whose pyrimidine nucleotide content was about 50% of the total purine and pyrimidine nucleotide liberated 0·4 equiv. of phosphoric acid groups per molecule of phosphorus after treatment with ribonuclease whereas calf-thymus and calf-pancreas pentosenucleic acids, which contain less than 40% of pyrimidine nucleotide, gave a corresponding figure of 0·25 equiv. per molecule of phosphorus which was similar to that given by yeast nucleic acid (Allen and Eiler, *J. Biol. Chem.*, 1941, **137**, 757; Schmidt, Cubiles, Swartz, and Thannhauser, *ibid.*, 1947, **170**, 759). Criteria for the hydrolytic action of ribonuclease differ considerably. Wiener, Duggan, and Allen (*ibid.*, 1950, **185**, 163) found that yeast nucleic acid lost 61·7% of organically combined phosphorus, rendered dialysable by ribonuclease hydrolysis. Zittle (*ibid.*, 1946, **163**, 119) showed that 23—33% of the total phosphorus of this nucleic acid was rendered soluble in 0·125% uranyl chloride (final concentration) in 2·5% trichloroacetic acid, a reagent which, under the conditions prevailing, does not precipitate mononucleotides. However, Tsuboi and Stowell (*Biochim. Biophys. Acta*, 1950, **6**, 192) claimed a 65·5% enzymic hydrolysis of their specimen of yeast nucleic acid, using this method, and 75% for a pentosenucleic acid derived from mouse liver. Carter and Cohn (*J. Amer. Chem. Soc.*, 1950, **72**, 2604) separated hydrolytic products from enzymically undegraded yeast nucleic acid by adjustment of the pH to 3·0 with hydrochloric acid; 73% of the total phosphorus was acid-soluble but part of this was polynucleotide in character. It thus appears (if one may summarise work which includes some without adequate characterisation of the substrate) that hydrolysis of yeast pentosenucleic acid with ribonuclease gives about 40% of polynucleotide (dialysable, and soluble in hydrochloric acid at pH 3·0) together with 20—30% of mononucleotides (largely pyrimidine, dialysable, soluble in hydrochloric acid at pH 3·0 and in 2·5% trichloroacetic acid containing 0·125% of uranyl chloride). Under Zittle's conditions, the three avian sarcomata pentosenucleic acids gave 59·3% (G.R.C.H. 15), 56·5% (Duran-Reynals "D"), and 56·5% (Rous No. 1) hydrolysis. The high ratio of purine to pyrimidine bases in these nucleic acids, therefore, does not lead to the suspicion that enzymic degradation had occurred before or during isolation.



——— *Nucleic acid from Rous No. 1 sarcoma*, pH 7·32.
– – – – *Nucleic acid from Duran-Reynals "D" sarcoma*, pH 6·81.

Separation, Identification, and Determination of Nucleosides.—The procedure for the quantitative hydrolysis of the nucleic acids to the component nucleosides followed exactly that described in Part I (*loc. cit.*), *viz.*, hydrolysis at 37° with 0·2N-sodium hydroxide followed by enzymic dephosphorylation of the nucleotides with prostatic acid phosphatase to nucleosides. The starch chromatograms were prepared and developed in the usual way. The nucleosides were identified by means of their absorption spectra in aqueous solution, by the characteristic spectral shifts on change of pH, and by their absolute and relative *R* values. The spectrophotometric methods available for the quantitative determination of the nucleosides have already been evaluated (Part I, *loc. cit.*), and for these analyses the method employing the combination of fractions comprising one chromato-

graphic band, evaporation to dryness *in vacuo*, and re-solution in 0·05N-hydrochloric acid was adopted. "Back-ground absorption" * was similarly determined. Table 1 compares the absolute and relative *R* values, and the analytical data are shown in Table 2.

Discussion.—The results leave no doubt that, like the other pentosenucleic acids which have been investigated, the two avian tumour nucleic acids described contain the four pentosides, adenosine, guanosine, cytidine, and uridine. The degree of recovery obtained in terms of hydrolysate nitrogen and phosphorus, and the sensitivity of the chromatographic procedure, render it extremely improbable that any component has been overlooked. There is little difference in the adenosine and guanosine content of the three nucleic acids. However, there is a considerable (29%) decrease in uridine content of the nucleic acid from Rous No. 1 sarcoma and a 17·5% increase in the cytidine content of that from Duran-Reynals "D" sarcoma compared with the G.R.C.H. 15 sarcoma. It is difficult to assess the significance, if any, of such variations. The other interesting feature of the three avian nucleic acids is the high guanine content which is thus far paralleled among mammalian pentosenucleic acids by that from calf-pancreas and from human-liver carcinoma (Volkin and Carter, *loc. cit.*; Chargaff *et al.*, 1950, *loc. cit.*). The general similarity between the composition of the latter and those here described may be significant, although the nucleic acid derived by Volkin and Carter (*loc. cit.*) from mouse hepatoma does not correspond. Should the preponderance of guanine be found to be characteristic of nucleic acids of some tumours in some animal species but not of others, a clue may be provided to the action of 8-azaguanine which has an inhibitory action on the growth of a number of transplantable mouse carcinomata and on some transplantable mouse lymphoid leukæmias. This inhibitory action was not manifested against mouse sarcomata, melanomata, or lymphosarcomata or against rat tumours (Kidder, Dewey, Parks, and Woodside, *Cancer Res.*, 1951, **11**, 204; Sugiura, Hitchings, Cavalieri, and Stock, *ibid.*, 1950, **10**, 178).

A preponderance of guanine in the isolated pentosenucleic acid may be presumed to imply a high demand for guanine, or guanine precursors, during cell growth, and it will be interesting to know whether the pentosenucleic acids of the mouse tumours which are inhibited in growth by 8-azaguanine have a different purine : pyrimidine composition from those derived from non-susceptible mouse tumours and whether such differences are paralleled in the deoxypentosenucleic acids from the same tissues.

Experimental

(With the assistance of J. F. Thomas.)

Preparation of Rous No. 1 Sarcoma Pentosenucleic Acid.—Acetone-dried sarcoma tissue (50 g.) was mixed with water (1 l.) in a Waring blendor for 1—2 minutes, and a few mg. of purified bovine-testis hyaluronidase (Armour Laboratories) in 2 c.c. of water were added. The action of the enzyme, which is extremely rapid at room temperature, was interrupted after a few minutes by addition of 1 l. of 4% aqueous phenol, and the tissue was allowed to undergo extraction for 24 hours at room temperature. The suspension was then centrifuged, and the deposit re-extracted with 1 l. of 2% phenol under the same conditions. The combined supernatant liquids were adjusted to 1% with respect to sodium chloride by addition of 20% sodium chloride and treated with alcohol (2 vols.), and the precipitate was collected, after chilling, by centrifugation. The deposit was thoroughly washed with 70% alcohol to remove traces of phenol, redissolved in 100 c.c. of 0·9% saline, the pH adjusted to 7·5 (glass electrode), and crystalline trypsin (30 mg., containing 50% of magnesium sulphate) added. The flask was "layered" with toluene and incubated at room temperature for 36 hours. The further purification of the nucleic acid then followed exactly the procedure already described for G.R.C.H. 15 pentosenucleic acid (Part I, *loc. cit.*). Two preparations gave: (1) (150 mg.) N (micro-Kjeldahl), 15·0%; P (micro-colorimetric), 8·1%; (2) (220 mg.) N, 14·9%; P, 7·6%. Both preparations were qualitatively free from protein and from deoxypentose.

Preparation of Duran-Reynals "D" Sarcoma Pentosenucleic Acid.—Two samples of this nucleic acid were prepared by the above method. Preparation 1 (166 mg.) gave N, 14·3; P, 7·9%. Preparation 2 (175 mg.) gave N, 14·3; P, 7·8%.

* *Errata.* In Part I, p. 1402, l. 3 from bottom, *for* "as above" *read* "unity"; p. 1403, l. 2, *for* "$E_1 = AB$; $E_2 = DE$" *read* "$xE_1 = AB$ and $xE_2 = DE$."

Action of Ribonuclease.—A solution (12 c.c.) of the nucleic acid (about 20 mg.) at pH 7·1 (glass electrode) was treated with a solution (1 c.c.) of crystalline ribonuclease (3 mg.). An aliquot part (1 c.c.) was taken immediately, 1 c.c. of 0·25% uranyl acetate in 5% trichloroacetic acid added, the mixture rapidly chilled, and the precipitated polynucleotide collected by centrifugation and washed. Analysis of both deposit and pooled supernatant liquids for organic phosphorus at zero time, after 1 hour's incubation at room temperature, and after an over-night treatment under the same conditions gave :

Time	Total precipitable P (mg.)	Hydrolysis, %	Time	Total precipitable P (mg.)	Hydrolysis, %	Time	Total precipitable P (mg.)	Hydrolysis, %
	Rous No. 1 sarcoma			G.R.C.H. 15 sarcoma			Duran-Reynals " D " sarcoma	
0	1·82	0	0	1·70	0	0	1·79	0
1 Hour	—	—	1 Hour	0·70	58·7	1 Hour	0·915	49·0
Overnight	0·79	56·5	Overnight	0·69	59·3	Overnight	0·665	56·5

Hydrolysis and Chromatography of the Pentosenucleic Acid of Rous No. 1 Sarcoma.—(A) The procedures used were exactly the same as those described in Part I (*loc. cit.*). The nucleoside hydrolysate was derived from 9·2 mg. of nucleic acid (Preparation 1). Flow data are given in Table 1 and the results in Table 2 (a).

(B) The nucleoside hydrolysate was here derived from 4·6 mg. of nucleic acid. Flow data are given in Table 1 and the results in Table 2 (b).

Hydrolysis and Chromatography of the Pentosenucleic Acid of Duran-Reynals " D " Sarcoma.—The nucleoside hydrolysate was derived from 4·55 mg. of nucleic acid. Flow data are given in Table 1 and the results in Table 2 (c).

TABLE 1. *Absolute and relative* R *values.*

Pentosenucleic acid	Starch col. (cm.)	Flow (c.c./h.)	Vol. (c.c.) at which band maximum occurred : Adenosine	Uridine	Guanosine	Cytidine
Rous A	19·5	2·2 ± 0·3	82	126	205	282
Rous B	20·0	2·6 ± 0·2	82	132	212	280
Duran-Reynals " D "	20·5	3·5 ± 0·2	84	138	214	302

	R (absolute)				*R* (relative)		
	Adenosine	Uridine	Guanosine	Cytidine	$R_U : R_A$	$R_G : R_A$	$R_C : R_A$
Rous A	0·75	0·49	0·30	0·22	0·65	0·40	0·29
Rous B	0·77	0·48	0·30	0·23	0·62	0·39	0·29
Duran-Reynals " D "	0·77	0·47	0·30	0·21	0·61	0·39	0·28

TABLE 2.

Nucleoside calc. as	Mg.	% of hydrolysate	N, as % of hydrolysate N	P, as % of hydrolysate P	Molar ratios	Mols. purine / Mols. pyrimidine
(a) *Analysis of Rous No. 1 pentosenucleic acid* (A, 9·2 mg.).						
Adenosine	0·843	9·17	16·03	13·1	1·0	4·45
Guanosine	3·085	33·58	55·40	45·3	3·45	
Uridine	0·475	5·17	3·96	8·1	0·62	2·72
Cytidine	1·588	17·29	19·94	27·3	2·10	
			95·3	93·8	—	1·64
(b) *Analysis of Rous No. 1 pentosenucleic acid* (B, 4·6 mg.).						
Adenosine	0·374	8·12	14·15	11·6	1·0	4·35
Guanosine	1·329	28·8	47·6	39·0	3·35	
Uridine	0·225	4·88	3·75	7·65	0·66	2·58
Cytidine	0·655	14·2	16·4	22·4	1·92	
			81·9	80·7	—	1·68
(c) *Analysis of Duran-Reynals " D " pentosenucleic acid* (4·55 mg.).						
Adenosine	0·311	6·85	12·6	10·05	1·0	4·61
Guanosine	1·192	26·30	45·4	36·32	3·61	
Uridine	0·258	5·68	4·57	9·13	0·91	3·27
Cytidine	0·669	14·70	17·80	23·80	2·36	
			80·4	79·3	—	1·41

The authors thank Mr. F. C. Middleton for his help with the spectrophotometry. This investigation has been supported by grants to the Royal Cancer Hospital and Chester Beatty Research Institute from the British Empire Cancer Campaign, The Jane Coffin Childs Memorial Fund for Medical Research, The Anna Fuller Fund, and the National Cancer Institute of the National Institutes of Health, United States Public Health Service. It was carried out during the tenure by one author (R. J. C. H.) of a Junior Research Fellowship from the British Empire Cancer Campaign.

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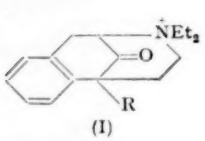
184. *Syntheses in the Morphine Series. Part III.* Further Experiments with β-Tetralone.*

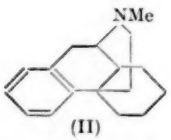
By J. A. BARLTROP and J. E. SAXTON.

β-Tetralone has been alkylated with 2-methoxyethyl chloride and with 2-dialkylaminoethyl chlorides, and the products have been transformed, by the Robinson–Mannich base ring-extension reaction, into hydrophenanthrenes substituted at $C_{(13)}$. Other experiments with β-tetralone are also described. A substance, probably (VII), possessing the morphine carbon–nitrogen skeleton has been prepared.

PART I of this series (*J.*, 1947, 399) describes methods devised for the synthesis of benzomorphan systems (I) from β-tetralone. This communication is largely concerned with attempts to extend these procedures to include the synthesis of derivatives of morphinan (II). Since substantial quantities of β-tetralone were required for these experiments, attention was directed to finding a satisfactory large-scale preparation of this substance. It soon became apparent that reduction of β-naphthol with sodium and liquid ammonia by a modification of Birch's method (*J.*, 1944, 430, and private communication) provided the best process.



(I)



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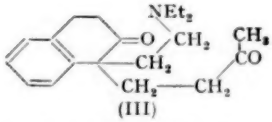
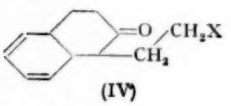
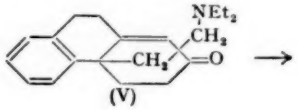


(III)

Attempts to alkylate β-tetralone with 2-dimethylaminoethyl chloride failed until it was discovered that success in this alkylation reaction was intimately connected with the quality of the sodamide employed as condensing agent. When purest sodamide was used, 1-2′-dimethylaminoethyl-1 : 2 : 3 : 4-tetrahydro-2-ketonaphthalene (IV; X = NMe_2) was obtained in 40% yield. However, the preparation of this substance was not realised until after the completion of the rest of the work described in this paper, which was, of necessity, performed on the more readily accessible diethylamino-analogue (IV; X = NEt_2). From this substance, we proposed to proceed by the reaction sequence :



(IV)



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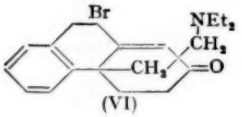
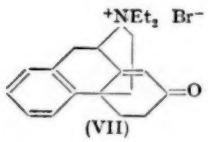


(VI)

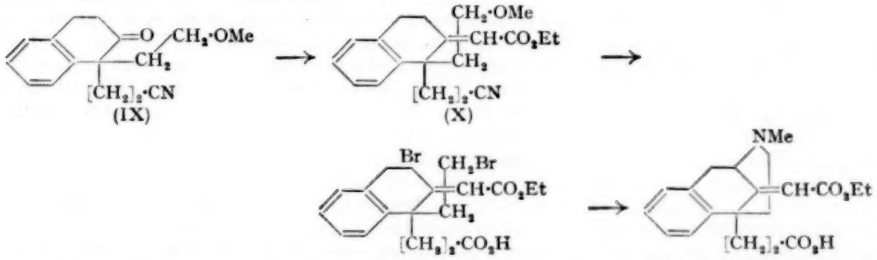


(VII)

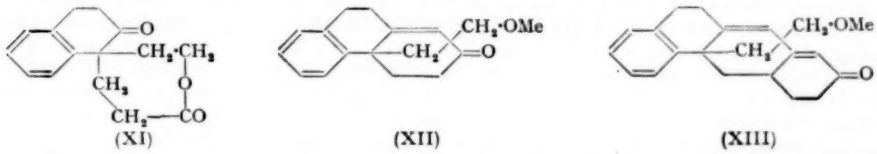
* Part II, *J.*, 1951, 2524.

The condensation of 1-alkyl-2-tetralones with diethylaminobutanone methiodide to give hydrophenanthrenes bearing angular substituents at $C_{(13)}$ has been used previously by Ghosh and Robinson (*J.*, 1944, 506) for the synthesis of substances related to morphine. We found no difficulty in applying the reaction to (IV; X = NEt_2) and obtained, in 20% yield, 13-2′-diethylaminoethyl-5 : 6 : 7 : 9 : 10 : 13-hexahydro-7-ketophenanthrene * (V), which has the same carbon skeleton as the methylmorphimethines, together with the uncyclised diketone (III). The exothermic reaction between (V) and *N*-bromosuccinimide gave, in addition to much polymeric material, a small quantity of a salt. Since αβ-unsaturated ketones are brominated preferentially in the allyl position by this reagent (*vide Chem. Reviews*, 1948, **43**, 283; Meystre and Wettstein, *Experientia*, 1946, **2**, 408), it is very likely that the brominated intermediate had the structure (VI). In Part I it has been established that in similar systems cyclisation of the nitrogen ring readily occurs and, by analogy, the morphinan structure (VII) is ascribed to the reaction product. Insufficient material was obtained for a structural proof to be possible.

It was hoped that the difficulties experienced in this route and the possible ambiguity associated with the bromination by *N*-bromosuccinimide might be avoided by an alternative scheme such as the following :



The starting material 1 : 2 : 3 : 4-tetrahydro-2-keto-1-2′-methoxyethylnaphthalene (IV; X = OMe) was readily prepared in a manner analogous to that of the corresponding amino-compounds, and acrylonitrile added smoothly to give (IX). The keto-group in this substance was sterically hindered, failing to react with semicarbazide or 2 : 4-dinitrophenylhydrazine, and this steric hindrance was responsible for the breakdown of the synthesis, for (IX) could not be caused to undergo a Reformatsky reaction. Another obstacle presented itself when (IX) was boiled with hydrobromic acid in an attempt to replace the methoxyl group by bromine. The product had the formula $C_{15}H_{16}O_3$. It was non-acidic but dissolved in warm sodium hydroxide solution; it did not decolourise bromine water and only slowly reacted with potassium permanganate solution. These facts can best be reconciled with the structure (XI), which contains a seven-membered lactone ring. This



formulation is supported by the infra-red absorption spectrum, which shows the absence of hydroxyl and ethylenic groups but possesses a fairly broad band of high absorption in the carbonyl region, which could be due to a carbonyl and a lactone grouping. There are very few analogies in the literature to this facile production of a monomeric ε-lactone.

Simultaneously with these experiments, (IV; X = OMe) was subjected to a Robinson ring-extension reaction. Two products were isolated. The main product, formed in 20% yield, was the expected 5 : 6 : 7 : 9 : 10 : 13-hexahydro-7-keto-13-2′-methoxyethylphen-

* This numbering is used to preserve relationship with the morphine alkaloids. Systematically, (V) should be named 12-2′-diethylaminoethyl-2 : 3 : 4 : 9 : 10 : 12-hexahydro-2-ketophenanthrene; similarly for other compounds in this paper.

anthrene (XII), but it was accompanied by a small amount of a substance $C_{21}H_{24}O_2$, probably the tetracyclic compound (XIII), arising from a ring extension of the primary product (XII). The formulation (XIII) is supported by the ultra-violet absorption spectrum [in ethanol; maximum at 2630 Å, log $\varepsilon = 4{\cdot}1$; cf. sorbaldehyde, $\lambda_{max.}$ (in ethanol) 2630 Å, log $\varepsilon = 4{\cdot}43$ (Braude, *Ann. Reports*, 1945, 115)].

Experimental

(M. p.s are uncorrected. Analyses are by Drs. Weiler and Strauss and Mr. F. C. Hall.)

β-*Tetralone.*—A suspension of β-naphthol (75 g.) in ethanol (70 c.c.) was cautiously added to liquid ammonia (800 c.c) contained in a well-lagged 3-litre flask with a plug of cotton wool in the neck. Sodium (33 g.) was added in small pieces with occasional stirring, during 1 hour. When the blue colour of the mixture had disappeared, ammonium chloride (78 g., 2·3 mols.) was added, and the remaining ammonia allowed to evaporate. Water (300 c.c.) was then added, and the solution acidified with concentrated hydrochloric acid. The β-tetralone was extracted with ether, purified *via* the bisulphite compound, and distilled. β-Tetralone (57 g., 80%) was collected at 139°/18 mm.

1-2′-*Dimethylaminoethyl*-1 : 2 : 3 : 4-*tetrahydro*-2-*ketonaphthalene.*—Dimethylaminoethyl chloride (8·2 g.) in toluene (50 c.c.) was condensed with β-tetralone (10 g.) in the presence of finely powdered, pure sodamide (2·8 g.) under the conditions described by Barltrop (*J.*, 1946, 962) for the preparation of the diethylaminoethyl analogue. The basic fraction, b. p. 115—135°/0·1 mm., was collected and redistilled. 1-2′-*Dimethylaminoethyl*-1 : 2 : 3 : 4-*tetrahydro*-2-*ketonaphthalene* (40%), a colourless oil, n_D^{20} 1·5394, was collected at 115—118°/0·05 mm. (Found: C, 77·3; H, 9·05; N, 6·3. $C_{14}H_{19}ON$ requires C, 77·4; H, 8·75; N, 6·45%).

Condensation between 1-*Diethylaminobutan*-3-*one and* 1-2′-*Diethylaminoethyl*-1 : 2 : 3 : 4-*tetrahydro*-2-*ketonaphthalene.*—Methyl iodide (8 g.) was added in portions to 1-diethylaminobutan-3-one (8 g.), contained in a 250-c.c. flask, with swirling and cooling in ice. After 1 hour at 0°, the crystalline methiodide was washed with ether. A cotton-wool plug was placed in the neck of the flask, a stream of dry nitrogen was passed through, and a solution of 1-2′-diethylaminoethyl-1 : 2 : 3 : 4-tetrahydro-2-ketonaphthalene (13 g.) in dry benzene added. The mixture was cooled in ice, a solution of potassium (4 g.) in absolute alcohol (60 c.c.) added, and the flask swirled and cooled in ice until all the methiodide had reacted. After 1½ hours at 0°, and then a further hour under reflux, the mixture was cooled and extracted with dilute hydrochloric acid. The basic products were isolated in the usual way, and distilled. A very viscous oil was collected at 160—180°/0·1 mm. Fractionation of the distillate gave two fractions: *A*, impure 1-2′-diethylaminoethyl-1 : 2 : 3 : 4-tetrahydro-2-keto-1-3′-ketobutyl-naphthalene (III), a pale yellow viscous oil (2 g.), b. p. 162—165°/0·06 mm., $n_D^{15\cdot5}$ 1·5416 (Found: C, 76·9; H, 9·4. $C_{20}H_{29}O_2N$ requires C, 76·2; H, 9·2%); *B*, 13-2′-*diethylaminoethyl*-5 : 6 : 7 : 9 : 10 : 13-*hexahydro*-7-*ketophenanthrene*, a pale yellow, viscous oil (3 g., 20%), b. p. 193—194°/0·2 mm., $n_D^{15\cdot5}$ 1·5572 (Found: C, 80·4; H, 9·4; N, 5·0. $C_{20}H_{27}ON$ requires C, 80·8; H, 9·1; N, 4·7%). The picrate crystallised from ethanol in yellow prisms, m. p. 200° (decomp.).

Reaction between (V) *and* N-*Bromosuccinimide.*—The above diethylaminoethylhexahydroketophenanthrene (2·5 g.) in boiling carbon tetrachloride (25 c.c.) was treated with *N*-bromosuccinimide (1·5 g.), added in small portions at intervals of 1 minute. The cooled and filtered reaction mixture was set aside for 3 days during which a gum was deposited. The carbon tetrachloride was decanted from the gum, which crystallised on trituration with dry *iso*propanol. *N*-*Ethyl*-7-*ketomorphin*-8-*ene ethobromide* (VII) (50 mg.) separated from *iso*propanol–ether in colourless crystals, m. p. 182° (Found: C, 63·5; H, 6·7; N, 3·6. $C_{20}H_{26}ONBr$ requires C, 63·8; H, 6·9; N, 3·7%). The salt was readily soluble in water and gave a deep red 2 : 4-dinitrophenylhydrazone.

1 : 2 : 3 : 4-*Tetrahydro*-2-*keto*-1-2′-*methoxyethylnaphthalene.*—A solution of β-tetralone (20 g.) and 2-chloroethyl methyl ether (12·3 g.) in toluene (100 c.c.) was vigorously stirred in an atmosphere of nitrogen, and finely powdered sodamide (5·2 g.) gradually added, so that the temperature of the reaction mixture remained below 35°. The temperature was then raised to 90° during 3½ hours and kept between 85° and 90° for a further 3 hours, after which the mixture was boiled under reflux for an hour. The cooled solution was washed with dilute hydrochloric acid, then twice with water, and dried and distilled. 1 : 2 : 3 : 4-*Tetrahydro*-2-*keto*-1-2′-*methoxyethylnaphthalene* (12·9 g., 47%) was collected at 104—108°/0·1 mm., as a colourless oil, n_D^{17} 1·5390 (Found: C, 76·2; H, 7·9. $C_{13}H_{16}O_2$ requires C, 76·5; H, 7·85%). The *semicarbazone*,

prepared in aqueous ethanol, crystallised from ethanol in colourless prisms, m.p. 150—151° (Found: C, 64·6; H, 7·15. $C_{14}H_{19}O_2N_3$ requires C, 64·4; H, 7·3%).

1-2′-Cyanoethyl-1 : 2 : 3 : 4-tetrahydro-2-keto-1-2′-methoxyethylnaphthalene.—A solution of acrylonitrile (3·25 g.) in dioxan (20 c.c.) was added dropwise during 20 minutes to a solution of the above ketone (12·5 g.) in dioxan (30 c.c.) to which had been added a 30% solution of potassium hydroxide in methanol (0·25 c.c.). The reaction mixture was vigorously stirred and cooled in ice. Stirring and cooling were continued for an hour, after which the solution was carefully neutralised with ethanolic hydrogen chloride, diluted with ether, and filtered. The solvent was removed, and the residual oil distilled. *1-2′-Cyanoethyl-1 : 2 : 3 : 4-tetrahydro-2-keto-1-2′-methoxyethylnaphthalene* (11 g., 75%), a colourless, viscous oil, n_D^{21} 1·5404, was collected at 176—178°/0·35 mm. (Found: N, 5·5. $C_{16}H_{19}O_2N$ requires N, 5·45%).

The Lactone of 1-2′-Carboxyethyl-1 : 2 : 3 : 4-tetrahydro-1-2′-hydroxyethyl-2-ketonaphthalene.—A solution of the above nitrile (2 g.) in concentrated hydrobromic acid (20 c.c.) and acetic acid (20 c.c.) was boiled under reflux for 8 hours. The solvents were then removed under reduced pressure, and the resulting solid was dissolved in sodium hydroxide solution. The filtered solution was acidified, and the precipitated solid was collected, dried, and crystallised from benzene (charcoal). The *lactone* (0·5 g., 25%) formed colourless prisms, m. p. 153—155° [Found: C, 73·5; H, 6·6; *M*, 245 (cryoscopic in camphor). $C_{15}H_{16}O_3$ requires C, 73·8; H, 6·6%; *M*, 244].

Condensation between Diethylaminobutanone and 1 : 2 : 3 : 4-Tetrahydro-2-keto-1-2′-methoxyethylnaphthalene.—Methyl iodide (12 g.) was added in portions to 1-diethylaminobutan-3-one (12 g.), cooled in a freezing mixture. After 1 hour, the crystalline methiodide was washed with ether by decantation. A cotton-wool plug was placed in the neck of a flask, a stream of dry nitrogen was passed through, and a solution of 1 : 2 : 3 : 4-tetrahydro-2-keto-1-2′-methoxyethylnaphthalene (15·5 g.) in dry benzene (60 c.c.) added. A solution of potassium (6·5 g.) in dry ethanol (60 c.c.) was then added, and the mixture swirled occasionally and allowed to remain in the freezing mixture until all the methiodide had reacted (*ca.* 2 hours). After a further hour, the mixture was heated under reflux for 2 hours, cooled, washed with dilute hydrochloric acid, dilute alkali, and finally with water, and dried. Distillation gave the following fractions: (i) b. p. 105—115°/0·1 mm., mainly unchanged starting material (1 g.); (ii) a colourless viscous oil (2 g.), b. p. 148—151°/0·12 mm., n_D^{21} 1·5800; (iii) a colourless viscous oil (4 g.), b. p. 151—160°/0·12 mm., n_D^{21} 1·5800; (iv) a colourless glass (2 g.), b. p. 185—195°/0·12 mm. Fractions (ii) and (iii) were impure *5 : 6 : 7 : 9 : 10 : 13-hexahydro-7-keto-13-2′-methoxyethylphenanthrene*, which was purified *via* the semicarbazone, and was obtained as a colourless oil, b. p. 150—155°/0·1 mm. (Found: C, 79·2; H, 8·0. $C_{17}H_{20}O_2$ requires C, 79·7; H, 7·8%); the *semicarbazone* formed prisms, m.p. 200°, from ethanol (Found: C, 68·7; H, 7·6; N, 13·5. $C_{18}H_{23}O_2N_3$ requires C, 69·0; H, 7·4; N, 13·4%). Fraction (iv) solidified on trituration with ether. Crystallisation from ethanol gave *3 : 4 : 6 : 7 : 8 : 9 : 12 : 13-octahydro-6-keto-13-2′-methoxyethyl-1 : 2-benzanthracene* (XIII) as colourless prisms, m. p. 122—124° (Found: C, 81·7; H, 7·6. $C_{21}H_{24}O_2$ requires C, 81·7; H, 7·8%). The *2 : 4-dinitrophenylhydrazone* crystallised from acetic acid in deep red plates, m. p. 227—228° (Found: C, 66·1; H, 5·7. $C_{27}H_{28}O_5N_4$ requires C, 66·4; H, 5·7%).

We are indebted to Dr. F. B. Strauss for the light-absorption data.

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185. *Picrotoxin and Tutin. Part IV.* The Reducing Properties and Functional Groups.*

By J. C. Benstead, H. V. Brewerton, J. R. Fletcher, M. Martin-Smith, S. N. Slater, and A. T. Wilson.

The paper is mainly concerned with an analysis of commonly accepted views of the nature of the picrotoxin series of compounds.

The evidence for the existence of a reducing system in the structures of picrotoxinin and related compounds is examined. It is concluded that, contrary to general opinion, these substances are not themselves reducing compounds but behave as such only if they are degraded to simpler, reducing compounds by the alkaline reagents used in the conventional tests.

The statement that picrotoxinin and picrotin are dilactones is shown to be based on evidence of doubtful validity. Other evidence bearing on this problem is discussed and experiments are described which lead unequivocally to the conclusion that there are two potential centres of acidity in these substances. Their formulation as dilactones is correct if potential acidity in this series is due solely to lactone groups.

The action of alkali on α-bromotutin yields an isomer and the same substance is obtained with diazomethane. The significance of this result is discussed in connection with the relationship of picrotoxinin to α-picrotoxinic acid.

The reaction of dihydropicrotoxinin with acetic anhydride in the presence of a trace of anhydrous ferric chloride gives a diacetyl derivative corresponding to the acetylation of a dihydric alcohol, rather than of a monohydroxy-ether.

Infra-red data are recorded and discussed.

Despite several important recent papers, much of the chemistry of picrotoxin and related substances is still obscure. Our own investigations are not yet complete but in view of two brief reports by Conroy (*J. Amer. Chem. Soc.*, 1951, **73**, 1889), which define the carbon skeleton of picrotoxinin and offer structural formulæ for this compound and its hydration products, we submit some account of our work.

The generally accepted view of the nature of picrotoxinin, $C_{15}H_{16}O_6$, and picrotin, $C_{15}H_{18}O_7$, is that they are dilactones with pronounced reducing properties. Meyer and Bruger (*Ber.*, 1898, **31**, 2958) state that an aqueous solution of picrotoxinin reduces ammoniacal silver nitrate in the cold and Fehling's solution on warming, but that picrotin does not reduce either reagent unless heated to about 70°. This statement is repeated by Horrmann (*ibid.*, 1910, **43**, 1903), and Mercer and Robertson (*J.*, 1936, 288) lay some stress on the strong reducing properties of dihydropicrotoxinin and dihydro*neo*picrotoxinin ("β-dihydropicrotoxinin"), as well as of picrotoxinin itself, in alkaline media. Similarly, α-picrotoxinic acid is credited with strong reducing properties (Meyer and Bruger, *loc. cit.*; Horrmann, *Ber.*, 1913, **46**, 2793; Sutter and Schlittler, *Helv. Chim. Acta*, 1950, **33**, 902). We have frequently observed in examining substances in this series for reducing properties that they are relatively stable to ammoniacal silver nitrate in the cold and, even on heating, reduction often does not take place readily. With ammoniacal silver nitrate sensitised by the addition of a little sodium hydroxide, reduction still does not in general take place in the cold, but does so extremely readily on heating. The fact being taken into account that heating of such substances as picrotoxinin, dihydropicrotoxinin, α-picrotoxinic acid, and dihydro-α-picrotoxinic acid with alkali (even aqueous sodium carbonate) causes profound decomposition to give reducing substances (Sutter and Schlittler, *Helv. Chim. Acta*, 1949, **32**, 1855, 1864; *loc. cit.*), it is clear not only that any reducing properties of picrotoxin and related substances have been exaggerated, but also that these properties may be due to the products of alkaline degradation rather than to the substances themselves. If this were correct there should be a correlation between stability towards alkali and reducing properties. This is indeed so. Of those derivatives of picrotin and picro-

* Part III, *J.*, 1949, 806.

toxinin which may be regarded as derived directly from them, the alkali-stable ones are α-picrototinic acid, picrotoxic acid, the bromopicrotoxinic acids, and Sutter and Schlittler's "Compound C" (*loc. cit.*, 1950). α-Picrotinic acid is non-reducing (Horrmann, *Ber.*, 1912, **45**, 3080); we have likewise found β-bromopicrotoxinic acid and "Compound C" to be non-reducing. Picrotoxic acid is described by Horrmann (*Annalen*, 1916, **411**, 273) as non-reducing but Harland and Robertson (*J.*, 1939, 937) refer to its strong reducing properties. We have found crude preparations of picrotoxic acid to show some reducing effect, due probably to unchanged picrotoxinin, but this effect is absent in well-purified specimens. Tables 1 and 2 record the behaviour of a range of substances in reduction

TABLE 1.

Compound	NH_3–$AgNO_3$	Sensitised NH_3–$AgNO_3$	Na_2CO_3
Ozonised *neo*picrotoxinin [1]	+		1
Glucose	+		3
*neo*Picrotoxinin	+		4
Ozonised picrotoxinin [2]	+		
*neo*Tutin [3]	+ (very slight)		5 [4]
Picrotoxin	+		4
Tutin	+ (slight)		6
α-Picrotoxinic acid	+ (very slight)		2
Cane sugar (comml.)	+ (trace)	1	
Acetyl*neo*picrotoxinin	+ (trace)	2	4
β-Bromopicrotoxinic acid	—	—	
"Compound C"	—	—	
Picrotoxic acid	—	—	
Methyl α-picrotinate	—	—	
Methyl β-picrotinate	—	—	

[1] This was the only substance tested which gave a positive result in the cold. [2] A specimen two years old. [3] Unpublished work. [4] Orange-red colour.

tests. Column 2 in each table gives the results of two sets of experiments in each of which the individual tests were carried out simultaneously, and the order of listing is that in which reduction of ammoniacal silver nitrate was first observed. Unless otherwise indicated a positive result implies marked reduction. It may be noted that if such substances as picrotoxinin, dihydropicrotoxinin, and picrotin are heated rapidly with an

TABLE 2.

Compound	NH_3–$AgNO_3$	Sensitised NH_3–$AgNO_3$	Na_2CO_3
Dihydro*neo*picrotoxinin	+		7
Dihydropicrotoxinin	+ (slight)		5
Bromo*neo*picrotoxinic acid	+ (trace)	2	3
Dihydro-α-picrotoxinic acid	+ (trace)	1	1
Picrotin	+ (slight)		2
Acetylpicrotin	+ (very slight)		6
α-Dihydrotutin	+ (slight)		4

ammoniacal silver nitrate solution which contains the smallest possible excess of ammonia they may be boiled for short periods without any reduction being observed. Col. 3 in each table lists the behaviour towards sensitised ammoniacal silver nitrate of those substances showing a negative or very slight positive effect in the first series of experiments. Each test was performed separately and the order of listing is an approximate indication of the extent of reduction.

The correlation between the existence of a group of alkali-stable compounds and their non-reducing properties is evident. An attempt was now made to gauge whether, in a group of alkali-unstable compounds, there is any correlation between the ease of degradation and the reducing power. Some indication is given by the observation that, although dihydropicrotoxinin is completely degraded by hot aqueous sodium carbonate, yet dihydrotutin under comparable conditions is only partly degraded (unpublished work). The latter (see Table 2) has but little effect on ammoniacal silver nitrate, but the former gives rapid evidence of some reduction. Again, although no difficulty has been experienced in converting bromopicrotoxinin into bromopicrotoxinic acid by the action of alkali, yet the corresponding reaction between bromo*neo*picrotoxinin and alkali (Slater, *J.*, 1949, 806)

must be conducted carefully to avoid alkaline degradation. It is noteworthy that, whereas β-bromopicrotoxinic acid appears in Table 1 as a non-reducing substance, yet bromo*neo*-picrotoxinic acid shows slight reducing properties. As a useful guide to the extent of degradation caused by alkali, one may take the development of the characteristic yellow colour which appears during the reaction. This is due to the formation of some as yet unisolated substance which is an indicator, being colourless in acid solution and yellow in alkali. The last columns in Tables 1 and 2 show the order in which the substances listed developed a certain arbitrary depth of yellow colour when heated with 2N-sodium carbonate at 100°, the tests being performed simultaneously. There is reasonable correlation between these columns and the second columns, if it is borne in mind that solubility factors probably affect the orders somewhat (*e.g.*, dihydropicrotoxinin and dihydro*neo*picrotoxinin dissolved very slowly in the carbonate test). The behaviour of α-picrotoxinic acid and dihydro-α-picrotoxinic acid is anomalous in that attack by carbonate is rapid whereas their reducing power is slight.

From the above results we conclude that the evidence for the existence of a reducing system in the structures of compounds of this series is better interpreted by the theory that any observed reduction is dependent on a preliminary degradation to simpler, reducing substances under the alkaline conditions of the tests used.

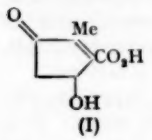
The evidence cited for the presence of two lactone groups in picrotoxinin and picrotin is most unconvincing. It was early observed (Paternò and Oglialoro-Todaro, *Gazzetta*, 1876, **6**, 531, and succeeding papers; Meyer and Bruger, *loc. cit.*, 1898) that picrotin, although unaffected by cold dilute aqueous sodium carbonate, dissolves in cold dilute aqueous sodium hydroxide and is recovered unchanged on acidification of this solution. This behaviour is typical of lactones (although not exclusively so). Under more drastic conditions picrotin, $C_{15}H_{18}O_7$, is converted irreversibly into the monobasic β-picrotinic acid, $C_{15}H_{20}O_8$, and finally into the dibasic picrotindicarboxylic acid, $C_{15}H_{22}O_9$ (Horrmann, *loc. cit.*, 1916). This addition of the elements of water is accompanied by the formation of new hydroxyl groups as revealed by Zerewitinoff determinations. Similarly, picrotoxinin, $C_{15}H_{16}O_6$, may be converted irreversibly into the monobasic α-picrotoxinic acid, $C_{15}H_{18}O_7$, and the dibasic picrotoxinindicarboxylic acid, $C_{15}H_{20}O_8$. On these ground picrotin and picrotoxinin have been regarded as dilactones. Unfortunately, as was clearly recognised by Horrmann (*loc. cit.*, 1916), the connection between the parent substances and their products of hydration is quite obscure. It has never been possible to isolate the true hydroxy-acids corresponding to picrotin and picrotoxinin. The only relationship of this sort yet established is between bromo*neo*picrotoxinin and the monobasic acid obtained by treating this substance with alkali (Slater, *loc. cit.*, 1949). Here we have the scheme :

$$\underset{C_{15}H_{16}O_6}{\text{Picrotoxinin}} \xrightarrow{H_2\text{-Pd-H}^+} \underset{C_{15}H_{16}O_6}{\textit{neo}\text{Picrotoxinin}} \underset{Zn}{\overset{Br_2}{\rightleftharpoons}} \underset{\substack{C_{15}H_{15}O_6Br \\ \text{(lactone)}}}{\text{Bromo}\textit{neo}\text{picrotoxinin}} \overset{OH'}{\underset{\text{Heat}}{\rightleftharpoons}} \underset{\substack{C_{15}H_{17}O_7Br \\ \text{(hydroxy-acid)}}}{\text{Bromo}\textit{neo}\text{picrotoxinic acid}}$$

We may state with certainty, therefore, that *neo*picrotoxinin (and hence presumably picrotoxinin) contains one lactone group. The close relationship between these two substances and picrotin (Slater and Wilson, *Nature*, 1951, **167**, 324) makes it equally probably that this also contains a lactone group.

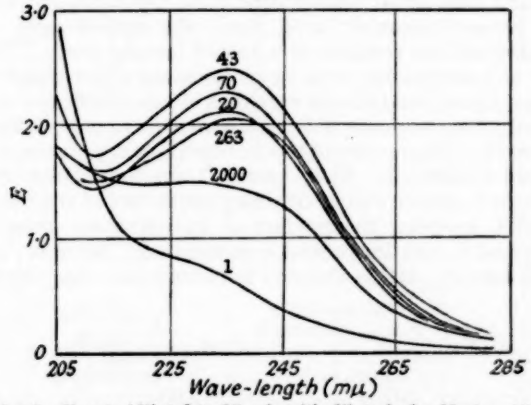
The question of the existence or otherwise of a second lactone group is much more difficult to answer. The recent demonstration by Sutter and Schlittler (*loc. cit.*, 1949) that picrotoxinin is extensively degraded by heating with aqueous sodium carbonate, and the application of this method to the splitting of dihydro*neo*picrotoxinin and picrotin (Slater and Wilson, *loc. cit.*), render suspect arguments based upon transformations under any but the mildest alkaline conditions. If we consider, for example, Horrmann's preparation of picrotindicarboxylic acid, in which picrotin was kept at room temperature with aqueous barium hydroxide for 3 days and then heated, it is plausible to suppose that under these conditions picrotindicarboxylic acid may well arise by profound internal modification of picrotin, or even complete degradation followed by interaction of the intermediate products formed. The carbonate degradation products of picrotin include the acid (I) which shows a characteristic absorption maximum in the ultra-violet at

235 mμ. With this as a guide to the progress of any alkaline degradation, picrotin was kept at room temperature with aqueous barium hydroxide and samples of the reaction mixture were removed from time to time. The absorption spectra of these samples are recorded in Fig. 1. The steady waxing and waning of the 235-mμ maximum is most striking and it is reasonable to attribute this to the formation and decay of an intermediate which contains a chromophore similar to that of (I). This intermediate reaches its maximum concentration after 2—3 days and is then consumed in some subsequent reaction. The amount of this compound formed is difficult to estimate accurately, as a knowledge of the absorption of other substances present is required. However, even a conservative estimate shows that a large proportion of picrotin has passed through the cycle. This could not be a subsidiary



(I)

FIG. 1.



Absorption curves of 1-*ml. aliquots* (*diluted to* 25 *ml. with dilute hydrochloric acid*) *removed after* x *hours from a reaction mixture containing picrotin* (0·5 *g.*) *in aqueous barium hydroxide* (0·75 *g. of barium hydroxide in* 15 *ml. of water*). *Measurements in cell of* d = 1 *cm.*

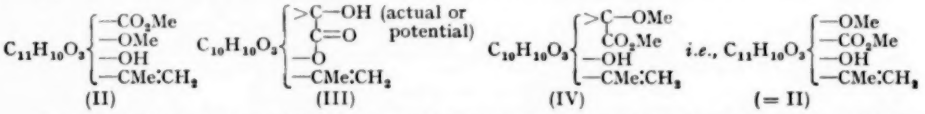
reaction in the light of the extremely high yield (96%) of picrotindicarboxylic acid obtained by Horrmann. If these views are correct it is no longer permissible to assume a simple relationship between picrotin and picrotindicarboxylic acid, and the chief cited evidence for the existence of a second lactone group in picrotin is invalidated.

If picrotindicarboxylic acid is not a simple derivative of picrotin, then the same may well be true of β-picrotinic acid. On the other hand, α-picrotinic acid could not be formed by the above mechanism, for it has been prepared in strongly oxidising solution (Horrmann, *Ber.*, 1912, **45**, 3434) which would be expected to destroy the intermediate. It can also be obtained from picrotin by acid hydrolysis (*idem*, *loc. cit.*, 1912). There is little experimental evidence on the relation of picrotoxinindicarboxylic acid to picrotoxinin.

The above discussion is intended to direct attention to the weakness of the argument on which presumably picrotin and picrotoxinin are formulated as dilactones. That alternative formulations are possible has, indeed, been pointed out (Harland and Robertson, *loc. cit.*, 1939). There is, however, other available evidence which does not yet appear to have been examined. The conversion of picrotin into α-picrotonic acid, $C_{15}H_{20}O_8$, and of picrotoxinin into picrotoxic acid, $C_{15}H_{18}O_7$, takes place under the influence of either acids or alkoxides (Horrmann, *locc. cit.*, 1912, 1916). There is evidence that these substances still behave towards alkali as lactones and, if it can be assumed that the newly-formed carboxyl and hydroxyl groups of these monobasic acids have come from a lactone group (their formation being accompanied by some other change as yet not understood), the parent substances would then be dilactones. Horrmann (*loc. cit.*, 1916) has stated that picrotoxic acid is resistant to attack by alkali and cannot therefore contain a lactone group. The position is actually the reverse, as was clear from this author's description of

the preparation of the methyl ester of picrotoxic acid, which was precipitated by acid from alkaline solution. This substance, although insoluble in cold dilute aqueous sodium carbonate, is readily soluble in cold dilute aqueous sodium hydroxide and is reprecipitated unchanged on acidification. Similarly, in the preparation of the methyl ester of α-picrotonic acid, the alkaline reaction mixture is acidified, whereupon the ester separates. Its behaviour towards alkali we have likewise found to be typically that of a lactone.

A third line of evidence can be followed in Sutter and Schlittler's recent paper (*loc. cit.*, 1950) dealing with the action of diazomethane on some substances in this series. It is known that diazomethane may attack lactones with formation of the methyl esters of the corresponding hydroxy-acids (Fischer and Hofmann, *Z. physiol. Chem.*, 1937, **245**, 139). In such reactions fundamental molecular rearrangements are unlikely to occur and it is interesting therefore that bromopicrotoxinin reacted with diazomethane in the presence of methyl alcohol to give the methyl ester of bromopicrotoxinic acid, presumably by attack of a lactone ring, and that under similar conditions α-picrotoxinic acid, the product of debromination of bromopicrotoxinic acid, gives the methyl ester of picrotoxinindicarboxylic acid, indicating the presence of a second lactone group. Inasmuch, however, as the relationship of α-picrotoxinic acid to picrotoxinin is not simply that of hydroxy-acid to lactone, this series of reactions we regard as of less significance than the reaction of picrotoxinin itself with diazomethane, which appears to us to provide the most satisfactory evidence yet published for the presence of two lactone rings in picrotoxinin. The substance produced, Sutter and Schlittler's " Compound C," was formulated by these workers as (II), but because of their difficulty in interpreting the nature of the residue $C_{11}H_{10}O_3$ they regarded Compound C as being the product of an extremely complex reaction. The formation of Compound C and its general behaviour can, however, be explained quite simply if the partial formula (III) is assigned to picrotoxinin and (IV) to Compound C.

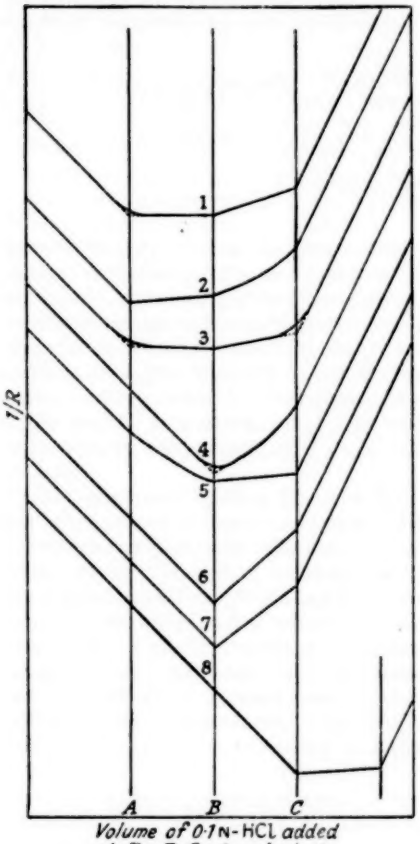


The methylation of alcoholic hydroxyl groups by diazomethane is possible if acidifying groups such as $-CO_2R$ are adjacent (Schmidt *et al.*, reported by Eistert in " Newer Methods of Preparative Organic Chemistry," p. 520; *Ber.*, 1934, **67**, 2120, 2127). If this scheme is correct, any postulated second lactone group must be present in the C_{11} residue, and its existence or otherwise should be clearly evident from the behaviour of Compound C. Although the reaction with cold dilute aqueous sodium hydroxide is sluggish, Compound C does indeed behave as a lactone, dissolving on long shaking and being reprecipitated unchanged on acidification.

As mentioned above, the methyl esters of picrotoxic and α-picrotinic acids are alkali-soluble and it was thought desirable to measure the potential acidity of these and other substances in this series quantitatively. Back-titration using indicators (phenolphthalein) has been used by other workers, and by this method picrotin appears to consume one equivalent of alkali in the cold (Horrmann, *loc. cit.*, 1910). Applied to the methyl ester of α-picrotinic acid, it showed 0·1 equiv. of alkali consumed per mole of ester, suggesting that the indicator used was unsuitable, and a more precise study, based on conductimetric titrations, was therefore undertaken. This yielded results of considerable interest which are summarised in Figs. 2 and 3. The curves of Fig. 2 all refer to substances which are recovered unchanged on acidification of their alkaline solution, and any conclusions drawn from the curves are therefore valid for the parent substances and not subject to any difficulties of interpretation through the occurrence of irreversible changes of an unknown and possibly profound nature. It is quite clear that picrotin and dihydropicrotoxinin contain two potential acidic groups, picrotoxic acid one such group in addition to the carboxyl group, and the methyl ester of α-picrotinic acid one. On the other hand, β-bromopicrotoxinic acid, bromo*neo*picrotoxinic acid, β-picrotinic acid, and dihydro-α-picrotoxinic acid show no acidity other than that due to their carboxyl groups. If potential acidity in this series can be attributed solely to the presence of lactone groups, we have in these

curves the first unequivocal evidence that picrotin and picrotoxinin are dilactones, and that one lactone group remains in their products of acid hydrolysis, α-picrotinic acid and picrotoxic acid, respectively. It may be noted that neither of these two acids has been converted into a stable dicarboxylic acid, and each has become stabilised towards the degradative action of alkali. On the other hand, in β-picrotinic acid and dihydro-α-picrotoxinic acid one of the lactone groups has been modified so that it is unaffected by cold dilute aqueous sodium hydroxide, although the instability towards more vigorous alkaline treatment is retained.

FIG. 2.

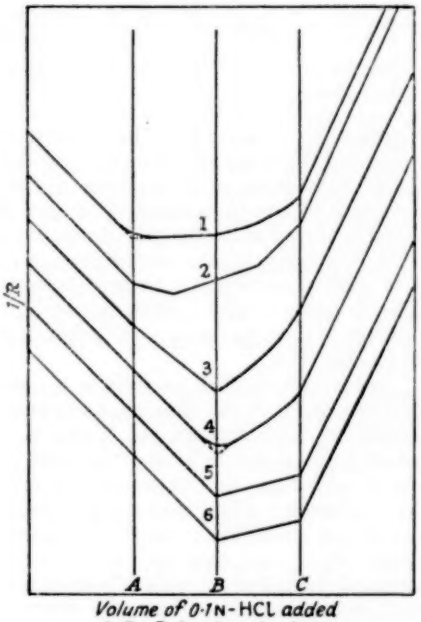


Volume of 0·1N-HCl added
A-B = B-C = 1 equivalent

1, *Picrotin.*
2, *Dihydropicrotoxinin.*
3, *Picrotoxic acid.*
4, *Dihydro-α-picrotoxinic acid.*
5, *Methyl ester of α-picrotinic acid.*
6, *β-Bromopicrotoxinic acid.*
7, *Bromoneopicrotoxinic acid.*
8, *Potassium salt of β-picrotinic acid.*

Schematic back-titration curves
(*see* p. 1050 *for actual values*).

FIG. 3.



Volume of 0·1N-HCl added
A-B = B-C = 1 equivalent

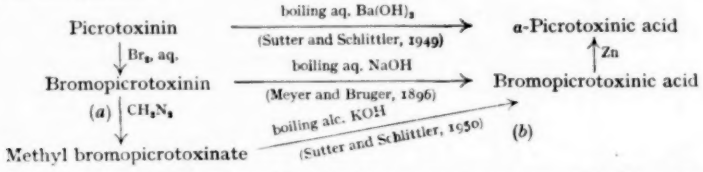
1, *Picrotoxinin.*
2, neo*Picrotoxinin.*
3, *Dihydroneopicrotoxinin.*
4, *α-Picrotoxinic acid.*
5, *Tutin.*
6, (α-)*Dihydrotutin.*

Schematic back-titration curves
(*see* p. 1050 *for actual values*).

The uncertain relationship between picrotoxinin and α-picrotoxinic acid has been referred to above. In spite of Sutter and Schlittler's assumption (*loc. cit.*, 1950) that the change from the former to the latter is simply the opening of a lactone ring, the evidence

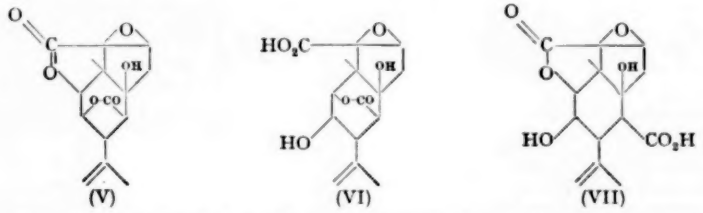
is clearly against this view and the above results serve to emphasize the difference. In particular we emphasize (i) the very different behaviour on titration of picrotoxinin and α-picrotoxinic acid on the one hand, and of dihydropicrotoxinin and dihydropicrotoxinic acid on the other; (ii) the hitherto apparently unrecognised reversible relationship between dihydropicrotoxinin and the dibasic acid (as yet unisolated) into which it is converted by cold dilute alkali; and (iii) the very different behaviour of picrotoxinin and α-picrotoxinic acid towards diazomethane.

The methods by which picrotoxinin has been converted into α-picrotoxinic acid are summed up in the scheme :



A noteworthy feature of all these methods is that each makes use of boiling alkali at some stage, and the suspicion arises that the rigour of this treatment may cause some irreversible change in addition to the opening of a lactone ring and that possibly these two effects are separated in the steps labelled (*a*) and (*b*). A closer investigation has shown, however, that the irreversible change is brought about under quite mild conditions; for instance, when bromopicrotoxinin is dissolved in dioxan and treated in the cold with a little alkali it is readily converted into bromopicrotoxinic acid; and the hydrolysis of the methyl ester is brought about immediately by suspending it in cold water and adding dilute aqueous sodium hydroxide. Furthermore, the acid formed regenerates the original ester on esterification.

The action of alkali on tutin is of considerable interest. It is clear from Figs. 2 and 3 that in going from picrotoxinin to bromopicrotoxinin there is an effective loss of one of the potentially acidic groupings. Tutin is titrated as a potentially monobasic acid, and it would be expected, following the close analogy so far revealed in the chemistry of tutin and picrotoxinin, that bromotutin would show *no* potential acidity. This is indeed the case. However, dilute aqueous sodium hydroxide is not without action on this substance—a (neutral) isomeride is readily produced and, furthermore, diazomethane has the same effect. It is clear that by a fortunate circumstance the dual action of alkali or diazomethane on bromopicrotoxinin (isomerisation and lactone opening) is modified in the case of bromotutin so that one effect (lactone opening) is eliminated while the other (isomerisation) remains operative. The complexity of the former reaction is thereby revealed.



Conroy (*loc. cit.*, 1951) has briefly discussed the relation of picrotoxinin to α-picrotoxinic acid in terms of their infra-red spectra. He also concludes that the acid is not a simple (chemical) hydrate of picrotoxinin, and traces the isomerisation effect to a change from a γ- to a δ-lactone system. The formulæ advanced for picrotoxinin, α-picrotoxinic acid, and picrotoxic acid are (V), (VI), and (VII), respectively.

The absence of any reducing group in these structures is in agreement with our own findings. The presence of two five-membered lactone rings in picrotoxinin is postulated on the basis of the split peak in the carbonyl absorption region of the infra-red spectra with maxima at 5·57 and 5·63 μ. The hydroxyl group gave a farly sharp band at 2·90 μ.

As the purely chemical evidence outlined above had left the problem of the number of lactone groups present dependent on the interpretation of the precise cause of potential acidity in this group, we also studied the infra-red spectra. This was made possible through the courtesy of Professor Roger Adams. The interpretation of the curves is complicated by the differences between the spectra of the solids and their solutions. When a Nujol mull of the solid was used, picrotin and *neo*picrotoxinin showed a split peak in the carbonyl region, whereas picrotoxinin itself showed only broad absorption. In dioxan solution, however, single bands were obtained in each case. For this reason Dr. E. M. Petersen, to whom we are greatly indebted for the infra-red data and their interpretation, concludes that the presence of a dilactone structure is doubtful.* The presence of a single five-membered lactone ring in each of the substances examined was inferred. The presence of the other functional groups, as deduced from the chemical evidence, is in accordance with the spectral characteristics.

Conroy's formulæ serve as a useful basis for further discussion, the complete definition of the carbon skeleton in particular being a major advance. Further experimental support appears necessary, and will no doubt be forthcoming, before the validity of the finer details of structure can be assessed. Attention may be drawn, however, to the over-simplification of the chemistry of picrotoxic acid implied by (VII). In particular: (i) The sole structural difference between picrotoxinin (V) and picrotoxic acid (VII) is attributed to the opening of a lactone ring: the very different behaviour of the two substances towards dilute alkali (see Figs. 2 and 3) implies some other structural difference. (ii) Picrotoxic acid is not attacked by alkali under conditions which bring about the fission of picrotoxinin: (VII) would be expected to undergo the Schlittler degradation. (iii) The characteristic bromination reaction of picrotoxinin and α-picrotoxinic acid might reasonably be expected to take place with (VII), but picrotoxic acid does not behave in this way.

Of the postulated functional groups there remains for discussion the ether linkage, conventionally assumed to be present to account for the inert oxygen atom of picrotoxinin and picrotin of otherwise undefined function. Here again positive evidence is lacking and it may be noted that no ether linkage has been found in any degradation product of established structure. Conroy's formulation assumes the presence of an ethylene oxide, which should presumably be capable of conversion into the corresponding glycol or a derivative. The simplest type of hydration is that usually brought about by the action of water at high temperatures. We have found, however, that picrotoxinin and dihydropicrotoxinin are recovered substantially unchanged after being heated with water at 150° (2 hours), and even at 200° (1 hour); although there is much obvious thermal decomposition, dihydropicrotoxinin is partly recovered. Another characteristic reaction of ethylene oxides is their conversion into the corresponding glycol diacetate under the influence of acetic anhydride and a trace of anhydrous ferric chloride (Knoevenagel, *Annalen*, 1914, **402**, 135). As applied to dihydropicrotoxinin, this reaction gave a quantitative yield of a diacetate, $C_{19}H_{22}O_8$, differing however by the elements of water from that expected if an oxide link had been attacked in the normal way, *viz.*, $C_{19}H_{24}O_9$. A dehydration accompanying the opening of the oxide link is unlikely since the substance gives no signs of unsaturation. Its formation, in fact, is most simply regarded as the acetylation of a dihydroxy-compound, and on this view dihydropicrotoxinin is a dihydric alcohol rather than a monohydroxy-ether. The substance is non-reducing and does not give a yellow colour when warmed with aqueous sodium carbonate.

The reaction of picrotoxinin itself and acetic anhydride in the presence of ferric chloride

* (Supplementary report by Dr. E. M. Petersen on the infra-red spectrum of a new specimen of picrotoxinin. Received, 28.1.52.) The infra-red spectrum in the 6 μ region of the new sample of picrotoxinin seems to have two bands in "Nujol" suspension and in solution instead of the one broad band which I observed before. The rest of the spectra are the same. The bands in the "Nujol" mull occur at 1787 and 1765 cm.$^{-1}$ (5·60 and 5·67 μ); they are strong and well resolved. In dioxan solution there is a strong band at 1802 cm.$^{-1}$ (5·55 μ) and a second band at 1793 cm.$^{-1}$ (5·58 μ). The latter band is not resolved into a sharp peak but is more of a shoulder on the 1802-cm.$^{-1}$ band. These different results may indicate that the new sample is purer than the original or that the sample preparation scattered more light in the first case, thus obscuring the band structure. In view of these new results and the chemical evidence there appear to be two lactone groups in picrotoxinin.

proceeded differently—on long storage in the cold a deep violet-purple colour slowly developed, suggesting the formation of an enol, but no pure material could be isolated from the product obtained by decomposing the reaction mixture with water.

Experimental

Reduction Tests.—A bulk sample of ammoniacal silver nitrate was prepared by adding aqueous ammonia (*d* 0·88) dropwise to 0·1N-aqueous silver nitrate until the precipitate dissolved and a slight excess of ammonia was present. The reagent was stable to heat. In the experiments summarised in the second columns of Tables 1 and 2 approximately equal small samples of the substances listed were heated with the ammoniacal silver nitrate in a water-bath (all tests in each group being done simultaneously), the time of heating being approximately 5 minutes to reach the boiling point of the bath which was then kept boiling for about 10 minutes. In the tests summarised in cols. 3 of Tables 1 and 2, each of which was carried out separately, a little of the bulk ammoniacal silver nitrate, containing a sufficient excess of ammonia to give reasonable stability to heat in the final reagent, was sensitised by adding a drop of aqueous sodium hydroxide prepared from AnalaR alkali. There sulting clear solution was stable to the conditions of heating used in the tests. Each test was performed by adding a small amount of substance, heating the mixture rapidly nearly to the boiling point, and continuing at this temperature for about 30 seconds.

Conductimetric Titrations.—A known weight of each substance was dissolved in a measured volume (excess) of 0·1N-sodium hydroxide, and the solution titrated in a semimicro-conductimetric cell by measuring the resistance. A continuous stream of previously purified air saturated with water vapour was bubbled through the solution to ensure effective stirring. The curves of Figs. 2 and 3 have been proportionately adjusted so that for all titrations the distances *AB* and *BC*, each representing one (theoretical) equivalent of alkali consumed by the substance titrated, are the same. The experimental values are given below. The molar concentrations of the solutions titrated varied slightly and any comparison of the relative slopes of the curves is subject to a corresponding small error. Although α-picrotoxinic acid is included in Fig. 3, it has on one occasion been recovered after acidification of the titration solution. Its stability towards alkali, however, is not so well marked as that of the dihydro-acid. Similarly, picrotoxinin has been recovered unchanged from solution in an excess of dilute alkali, although not under the controlled experimental conditions of the recorded back-titrations. Dihydropicrotoxinin, however, is reasonably stable to cold dilute alkali and is always recovered on acidification. The curve for *neo*picrotoxinin is difficult to interpret. It is reproducible.

Data for Figs. 2 and 3.

Substance (Fig. 2)	Wt., mg.	G.-mols. × 10^4	NaOH consumed, g.-equiv. × 10^4 A–B	B–C	Total	Number of actual or potential acidic groups
Picrotin	46·5	1·50	1·36	1·60	2·96	2
Dihydropicrotoxinin	36·8	1·25	1·30	1·20	2·50	2
Picrotoxic acid	43·2	1·39	1·30	1·40	2·70	2
Dihydro-α-picrotoxinic acid	30·1	0·964	0	0·93	0·93	1
Methyl α-picrotinate	41·0	1·20	0	1·23	1·23	1
β-Bromopicrotoxinic acid	22·7	0·584	0	0·55	0·55	1
Bromo*neo*picrotoxinic acid	83·5	2·14	0	2·25	2·25	1
Potassium β-picrotinate	24·3	0·665	0	0	0	0
Fig. 3.						
Picrotoxinin	45·3	1·55	1·55	1·55	3·10	2
*neo*Picrotoxinin	38·5	1·32	—	—	2·60	2
Dihydro*neo*picrotoxinin	25·8	0·878	0	0·85	0·85	1
α-Picrotoxinic acid	29·2	0·943	0	0·90	0·90	1
Tutin	34·6	1·18	0	1·30	1·30	1
(α-)Dihydrotutin	38·3	1·30	0	1·35	1·35	1

Action of Alkali on Bromotutin.—α-Bromotutin was shaken with a known slight excess of 0·1N-sodium hydroxide (calculated on the assumption that α-bromotutin was a potential monobasic acid). After 15 minutes a flocculent precipitate appeared suddenly. The mixture was kept for some hours, and the precipitate then collected and crystallised from methyl alcohol. The *substance* melted at 267° (Found: C, 48·1; H, 4·94; Br, 21·7. $C_{15}H_{17}O_9Br$ requires C, 48·3; H, 4·60; Br, 21·4%). The aqueous mother-liquor from the above preparation on titration showed no loss of alkali.

Action of Diazomethane on Bromotutin.—An excess of an ethereal solution of diazomethane

was added to α-bromotutin (220 mg.), and the mixture kept at room temperature for 60 hours. The resulting solution was evaporated to half volume and set aside. The crystalline material which separated melted at 210°, raised to 268° after three crystallisations from ethyl alcohol. It showed no mixed m. p. depression with the above substance.

Acetylation of Dihydropicrotoxinin.—Dihydropicrotoxinin (0·5 g.) was kept for a week at room temperature with an excess of acetic anhydride containing sufficient anhydrous ferric chloride to give the solution a pale yellow colour. After addition of water, the *diacetate* (0·5 g.) slowly separated and had m. p. 243—244°, raised to 245° by crystallisation from methyl alcohol (Found: C, 60·1, 60·15; H, 5·87, 5·85; Ac, 21·3. $C_{19}H_{22}O_8$ requires C, 60·31; H, 5·82; 2 Ac, 22·8%).

REPORT ON THE INFRA-RED SPECTRA OF PICROTOXININ, PICROTIN, AND *neo*PICROTOXININ.

By E. M. PETERSEN (University of Illinois).

Picrotoxinin.—The spectrum shows an unconjugated C=C bond at 1649 cm.$^{-1}$ (6·06 μ). In the solid state the C=O absorption is broad and not well resolved, ranging from 1790 to 1766 cm.$^{-1}$ (5·59—5·66 μ); however, in dioxan solution the C=O linkage appears as a single band at 1799 cm.$^{-1}$ (5·58 μ). This result would indicate one lactone system. A strong free hydroxyl absorption appears at 3464 cm.$^{-1}$ (2·89 μ) in the solid, and at 3410 cm.$^{-1}$ (2·93 μ) in the dioxan solution. The spectrum shows very strong absorption at 1163 cm.$^{-1}$ (8·60 μ) which is in the range of the C–OH vibrations of tertiary alcohols.

Picrotin.—The spectrum shows no C=C absorption. In the Nujol mull two bands appear at 1803 and 1773 cm.$^{-1}$ (5·55 and 5·64 μ). The 1773 band is stronger. However, in solution, one band appears at 1799 cm.$^{-1}$ (5·58 μ) in dioxan and at 1794 cm.$^{-1}$ (5·57 μ) in nitromethane or methanol. The OH absorption in the Nujol spectrum indicates the possibility of more than one OH since there is a band at 3333 cm.$^{-1}$ (3·00 μ) and a weaker broad band at 3120 cm.$^{-1}$ (3·21 μ). In dioxan solution one broad band appears at 3332 cm.$^{-1}$ (3·00 μ). There is no strong absorption at 1163 cm.$^{-1}$ (8·60 μ) as in picrotoxinin, but a fairly strong band appears at 1158 cm.$^{-1}$ (8·64 μ) which is also in the range of tertiary alcohols. The possibility of a dilactone structure seems rather doubtful since the C=O absorption is not high enough.

neoPicrotoxinin.—The spectrum of the solid shows two well-resolved bands at 1803 and 1763 cm.$^{-1}$ (5·55 and 5·67 μ). This would seem to indicate two lactone systems. However, in solution only one C=O absorption appears, again in about the same place as in picrotoxinin and picrotin. No C=C absorption appears. One sharp strong OH absorption band appears at 3497 cm.$^{-1}$ (2·86 μ) in the solid and at 3390 cm.$^{-1}$ (2·95 μ) in the solution. The 3497 cm.$^{-1}$ band is high enough to indicate almost no bonding of the OH.

The shift of the carbonyl bands of these three compounds to approximately the same frequency in solution is difficult to explain. It may possibly be due to a high degree of association in the solid which is not present in solution. The solution spectra would indicate that the lactone systems of the compounds are similar and are most probably five-membered saturated lactones.

Note (by S. N. SLATER).—The absence of C=C absorption in *neo*picrotoxinin may be correlated with its formulation as a tetra-substituted olefin (Slater, *loc. cit.*, 1949), although the work of Slater and Wilson (*loc. cit.*, 1951) shows clearly that the system present must be a simple *iso*propylidene one. Jones *et al.* (*J. Amer. Chem. Soc.*, 1950, **72**, 86) have shown that the band normally observed in the region 1580—1680 cm.$^{-1}$, which is due to the stretching motion of the C=C bond, may be absent, *e.g.*, in unconjugated $\Delta^{8:14}$ and $\Delta^{9:11}$ compounds of the steroid series.

Two of us (H. V. B. and A. T. W.) acknowledge the tenure of senior bursaries from the Public Service Commission, and one of us (M. M.-S.) the tenure of a Sir George Grey Scholarship. Thanks are due to the Director of the Dominion Laboratory for the use of certain facilities. We are grateful to Messrs. T. H. Kennedy and J. Murray for helpful suggestions and discussions on the action of diazomethane on hydroxy-lactones, and to Professor E. Schlittler for generously informative correspondence. The micro-analyses are by the Microchemical Laboratory of the Chemistry Department of the University of Otago, under the supervision of Dr. T. S. Ma and Mr. A. D. Campbell. The work has been assisted by a grant from the Research Fund of the University of New Zealand.

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[*Received, May 21st*, 1951.]

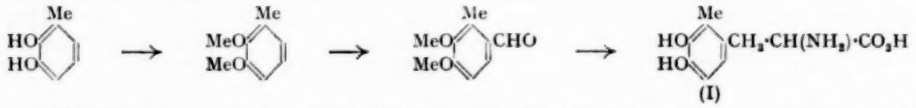
186. *Melanin and its Precursors. Part IV.* Synthesis of β-3 : 4-Dihydroxy-2- and -5-methylphenylalanine.*

By R. I. T. Cromartie and John Harley-Mason.

β-3 : 4-Dihydroxy-2- and -5-methylphenylalanine have been synthesised by conventional methods starting from 3-methylcatechol and *o*-vanillin respectively.

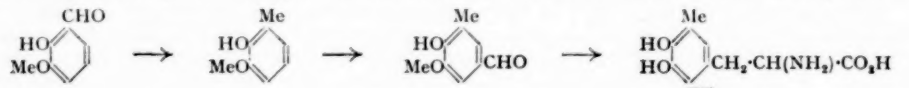
In Part III * the conversion of β-3 : 4-dihydroxyphenylalanine into 5 : 6-dihydroxyindole was described. In this paper the synthesis of β-3 : 4-dihydroxy-2- (I) and -5-methylphenylalanine (II) are described : their conversion into methylated 5 : 6-dihydroxyindoles will be recorded later.

3-Methylcatechol requires a large excess of methyl sulphate for conversion into the dimethyl ether, the hydroxyl group *ortho* to the methyl group apparently being sterically hindered. Treatment of the dimethyl ether with hydrogen cyanide and aluminium chloride gave 3 : 4-dimethoxy-2-methylbenzaldehyde, first obtained from cryptopine (Perkin, *J.*, 1916, **109**, 915); the derived azlactone was ring-opened by sodium hydroxide to give α-benzamido-3 : 4-dimethoxy-2-methylcinnamic acid, which with boiling hydriodic acid and red phosphorus afforded the amino-acid (I).



(I)

o-Vanillin was reduced to 3-methylcatechol 1-methyl ether by a modification of Koetschet's method (*Helv. Chim. Acta*, 1930, **13**, 476) and converted into 4-hydroxy-3-methoxy-5-methylbenzaldehyde as described by the same author. This aldehyde was



(II)

converted into an azlactone with hippuric acid and acetic anhydride, the phenolic hydroxyl group being acetylated in the process. Treatment with sodium acetate in ethanol effected ring-opening and esterification, giving ethyl 4-acetoxy-α-benzamido-3-methoxy-5-methylcinnamate which with hydriodic acid and red phosphorus gave the amino-acid (II).

Experimental

2 : 3-*Dimethoxytoluene.*—To a boiling solution of 3-methylcatechol (62 g.) and sodium hydroxide (200 g.) in water (800 c.c.) methyl sulphate (266 g.) was added slowly under nitrogen. After the addition was complete, boiling was continued for 2 hours and then a further amount of methyl sulphate (266 g.) added as before. After a further 2 hours' boiling the mixture was cooled and extracted with ether, the extract dried, and the solvent removed. The residual 2 : 3-dimethoxytoluene (52 g.) distilled at 56—60°/1 mm.

3 : 4-*Dimethoxy-2-methylbenzaldehyde.*—Finely powdered aluminium chloride (28 g.) was covered with benzene (20 c.c.) and cooled in ice while 2 : 3-dimethoxytoluene (25 g.) was added slowly with stirring. A solution of anhydrous hydrogen cyanide (17·5 g.) in benzene (25 c.c.) was then added. A slow stream of hydrogen chloride was passed into the mixture, which was warmed under reflux in a thermostatic bath kept at 30°, for 8 hours. The mixture was decomposed with concentrated hydrochloric acid (100 c.c.) and ice (200 g.) and then boiled to remove excess of hydrocyanic acid. After cooling, the mixture was extracted with ether (2 × 250 c.c.), and the ethereal solution shaken with sodium hydrogen sulphite solution. When the sulphite solution was made alkaline, 3 : 4-dimethoxy-2-methylbenzaldehyde (20 g.) was precipitated. Recrystallisation from light petroleum (b. p. 40—60°) gave long colourless needles, m. p. 50° (Found : C, 67·1; H, 6·9. Calc. for $C_{10}H_{12}O_3$: C, 66·7; H, 6·7%; Perkin (*loc. cit.*) gives m. p. 52—53°. The oxime formed colourless needles from light petroleum (b. p. 60—80°), m. p.

* Part III, *J.*, 1951, 2248.

96° (Found: C, 62·1; H, 6·9. Calc. for $C_{10}H_{13}O_3N$: C, 61·6; H, 6·7%); Perkin (*loc. cit.*) gives m. p. 98—99°.

β-3 : 4-*Dihydroxy*-2-*methylphenylalanine* (I).—3 : 4-Dimethoxy-2-methylbenzaldehyde (10 g.), hippuric acid (10·5 g.), anhydrous sodium acetate (4·8 g.), and acetic anhydride (18 c.c.) were mixed and heated at 100° for 2 hours. Ethanol (25 c.c.) was then added with stirring and the mixture kept overnight at 0°. The 4-(3 : 4-*dimethoxy*-2-*methylbenzylidene*)-2-*phenyloxazolone* (10·5 g.) which had separated was collected and washed with a little cold ethanol and then with boiling water. Recrystallisation from benzene–light petroleum afforded bright yellow prisms, m. p. 246° (Found: C, 70·8; H, 5·3. $C_{19}H_{17}O_4N$ requires C, 70·6; H, 5·3%).

To a solution of the oxazolone (9 g.) in warm ethanol (22 c.c.) 5% sodium hydroxide solution (22 c.c.) was added and the mixture heated for 15 minutes at 100°. After cooling, 20% hydrochloric acid was added until the solution was just acid to litmus and after 3 hours the precipitated α-*benzamido*-3 : 4-*dimethoxy*-2-*methylcinnamic* acid (7·5 g.) was collected and recrystallised from aqueous ethanol, giving colourless plates, m. p. 226—228° (decomp.) (Found: C, 67·3; H, 6·0. $C_{19}H_{19}O_5N$ requires C, 66·9; H, 5·6%).

The foregoing acid (11·2 g.) was boiled under reflux for 2½ hours with acetic anhydride (67 c.c.), hydriodic acid (*d* 1·7; 67 c.c.), and red phosphorus (6·7 g.). After cooling, water (120 c.c.) was added and the phosphorus filtered off. The solution was extracted with ether (3 × 100 c.c.) to remove benzoic acid and iodine and then evaporated to dryness in a vacuum. Water (200 c.c.) was added to the residue and the evaporation repeated. The last traces of hydriodic acid were removed at 100° in a high vacuum. The crystalline residue was dissolved in water (40 c.c.) and adjusted to pH 5 by addition of saturated sodium acetate solution. A little sodium dithionite was added to retard oxidation and after 4 hours a small amount of amorphous precipitate was filtered off. The filtrate was allowed to evaporate slowly in a vacuum-desiccator, β-3 : 4-*dihydroxy*-2-*methylphenylalanine* (3·5 g.) crystallising during several days. The acid recrystallised from water containing sulphur dioxide as small colourless plates, m. p. 186—192° (decomp.), containing a molecule of water of crystallisation not removed at 70°/1 mm. (24 hours) (Found: C, 52·5; H, 6·6; N, 6·2. $C_{10}H_{13}O_4N,H_2O$ requires C, 52·4; H, 6·55; N, 6·1%).

3-*Methylcatechol* 1-*Methyl Ether*.—Amalgamated zinc (150 g.) was placed in a flask fitted with a Vigreux column and condenser and two dropping funnels. The zinc was covered with a mixture of concentrated hydrochloric acid and water (2 : 1), and the mixture boiled so that slow distillation occurred. *o*-Vanillin (45 g.) heated to just above its m. p. was run in from one funnel at the same rate as the product distilled and hydrochloric acid of the same strength added from the other funnel as required. Distillation was continued until no more oily drops poured over (about 5 hours). The distillate was extracted with ether, the ethereal solution shaken with sodium hydrogen sulphite solution to remove *o*-vanillin, and dried, and the ether removed, leaving 3-methylcatechol 1-methyl ether (35 g.) as large prisms.

β-3 : 4-*Dihydroxy*-5-*methylphenylalanine* (II).—4-Hydroxy-3-methoxy-5-methylbenzaldehyde (Koetschet, *loc. cit.*) (8·5 g.), hippuric acid (10·3 g.), anhydrous sodium acetate (4·4 g.), and acetic anhydride (25 c.c.) were heated at 100° for 2 hours. Ethanol (25 c.c.) was then added and the whole kept overnight at 0°. 4-(4-*Acetoxy*-3-*methoxy*-5-*methylphenyl*)-2-*phenyloxazolone* (9·5 g.) which had separated was collected and washed with a little ethanol and then with boiling water. Recrystallisation from ethanol afforded yellow plates, m. p. 164—165° (Found: C, 68·2; H, 5·0. $C_{19}H_{17}O_5N$ requires C, 67·2; H, 5·0%).

The oxazolone (13·5 g.), fused sodium acetate (6 g.), and absolute ethanol (300 c.c.) were boiled under reflux for 3 hours. The cooled solution was poured into water (1 l.) and kept overnight at 0°. The *ethyl* 4-*acetoxy*-α-*benzamido*-3-*methoxy*-5-*methylcinnamate* (11·2 g.) which had separated was collected and formed colourless plates (from ethyl acetate–light petroleum), m. p. 142° (Found: C, 66·1; H, 6·0. $C_{22}H_{23}O_6N$ requires C, 66·5; H, 5·8%). The ester (8·7 g.), hydriodic acid (*d* 1·7; 53 c.c.), acetic anhydride (53 c.c.), and red phosphorus (5·3 g.) were refluxed for 2·5 hours and worked up as described above for the isomeric acid, to give β-3 : 4-*dihydroxy*-5-*methylphenylalanine* (2 g.) which decomposed without melting above 180° (Found: C, 52·7; H, 6·5; N, 5·8. $C_{10}H_{13}O_4N,H_2O$ requires C, 52·4; H, 6·55; N, 6·1%).

One of us (R. I. T. C.) thanks the Department of Scientific and Industrial Research for a Maintenance Grant.

UNIVERSITY CHEMICAL LABORATORY, CAMBRIDGE. [*Received, November 17th*, 1951.]

187. *Wood Starches. Part II.* The Structure of the Sapwood Starch of the Maple* (Acer *Spp.*).

By Clinton E. Ballou and (the late) E. G. V. Percival.

Maple sapwood starch has been shown to contain *ca.* 19% of amylose. The methylated derivative, of high molecular weight, gave tetramethyl glucopyranose (3·3—3·4%), 2 : 3 : 6-trimethyl glucose (92—93%), and dimethyl glucoses (4—5%) on hydrolysis, corresponding to an average chain length of 26 glucose units for the amylopectin fraction. Periodate oxidation gave a somewhat lower figure (22 units) for this fraction.

In continuation of the investigations on wood starches,* a study has been made of a specimen of maple sapwood starch kindly supplied by Mr. W. G. Campbell, Forest Products Research Laboratory of the Department of Scientific and Industrial Research, Princes Risborough.

The light brown specimen (moisture content 15%; $[\alpha]_D$ +185° in perchloric acid) was purified by extraction with aqueous methanol (85%) which removed *ca.* 2·5% of the dry weight of the sample as a brown oil. Then, after hydrolysis with sulphuric acid (2%), an insoluble residue (10·5%) remained. The starch content, calculated from the reducing value of the hydrolysate, amounted to 86% of the dry weight. Chromatographic examination revealed the presence of glucose (96·4%) and xylose (3·6%), presumably derived from an accompanying xylan, so that the true starch content was *ca.* 84%.

The amylose content of the maple starch was found to be 16·5% (from the blue value), but the more accurate potentiometric titration method (Part I *) gave a value of 19%. Because of the limited supply of starch available, fractionation into amylose and amylopectin was not attempted. It may be recorded, however, that a typical crystalline amylose–butanol complex was isolated from a specimen of oak sapwood starch.

Determination of the proportion of non-reducing terminal groups by periodate oxidation (Brown, Halsall, Hirst, and Jones, *J.*, 1948, 27) gave an average chain length of 22 glucose units, compared with a value of 20 units determined by the same method for elm sapwood starch.

Methylated maple starch was found to have an apparent molecular weight of *ca.* 440 000 by the viscosity method. Hydrolysis of this product gave the following sugars as identified and estimated on the paper chromatogram (Part I *): tetramethyl glucopyranose (3·4%), 2 : 3 : 6-trimethyl glucose (91·6%), 2 : 3-dimethyl xylose from the contaminating xylan, 2 : 3-dimethyl glucose (5%), and a trace of another dimethyl glucose. The average chain length for the amylopectin component of the maple sapwood starch is therefore *ca.* 26 units.

Confirmation of this result and more precise identification of the products of hydrolysis were obtained by separating the products of hydrolysis on the cellulose column (Part I *) whence crystalline tetramethyl glucopyranose (3·3%), crystalline 2 : 3 : 6-trimethyl glucose (92·9%), and syrupy dimethyl glucoses (3·8%) were obtained.

The results of this investigation reveal that maple sapwood starch displays no unusual features, if the presence of xylose in the hydrolysed material is attributed to an associated xylan. The amylose content is similar to that of elm starch, and the fact that the amylopectin component has a larger average chain length is by no means surprising when it is recalled that the values recorded for other plant amylopectins vary from 20 units in maize and banana to 26 units in potato, sweet potato, and arrowroot amylopectins (Brown, Halsall, Hirst, and Jones, *J.*, 1948, 27).

Experimental

General Properties of Maple Sapwood Starch.—The starch was light brown and granular, and had $[\alpha]_D$ +185° (*c*, 1·0 in perchloric acid). The moisture content was 15%. Exhaustive extraction of the dry starch with boiling aqueous methanol (85%; 250 c.c.) in four operations

* Part I, *J.*, 1951, 3489.

removed *ca.* 2·5% of a dark brown oil. All subsequent work was carried out on this extracted material.

Hydrolysis.—The starch (91·6 mg.) was heated for 7 hours at 100° in a sealed tube with sulphuric acid (5 c.c.; 2%) containing acetic acid (2 drops). The undissolved material (9·78 mg.) was removed and the filtrate was neutralised with barium carbonate and diluted to 100 c.c. 5 C.c. consumed 2·47 c.c. of 0·0197N-iodine in the determination of aldose sugars by hypoiodite. From this result and with correction for the insoluble material (10·5%) the starch content of the sample was calculated to be 86·1%. The hydrolysate was deionised and examined on the paper chromatogram with the butanol–ethanol–water–ammonia solvent (Partridge, *Biochem. J.*, 1948, **42**, 238). Quantitative determinations gave 96·4% of glucose and 3·6% of xylose.

Chromatography with the acetic acid–ethyl acetate–water solvent (Jermyn and Isherwood, *Biochem. J.*, 1949, **44**, 402) gave glucose, xylose, and a faint trace of arabinose.

Periodate Oxidation.—Starch (0·2430 g.) in water (52·5 c.c.) containing potassium chloride (2·5 g.) was shaken in the dark with sodium periodate (7·5 c.c.; 0·293M) (Halsall, Hirst, and Jones, *J.*, 1947, 1427). The formic acid released was titrated after 168 hours (10 c.c. required 0·90 c.c. of 0·00943N-sodium hydroxide) and 192 hours (0·93 c.c.). The release of formic acid after 168 hours corresponds to 21·9 glucose units per end group, after correction for the amylose and the non-carbohydrate material. On the assumption that 5% of lignin was present, and with a correction for the acidic material produced on periodate oxidation, the chain length would be *ca.* 27 glucose units on the basis of the experiments described previously (Part I, *loc. cit.*).

Determination of the Amylose Content.—(a) *Colorimetrically.* Higginbotham and Morrison's method (*J. Text. Inst.*, 1949, **40**, T208) gave a blue value of 0·210. Based on a blue value of 1·40 for amylose this corresponds to an amylose content of 16·5% after correction for the non-starch components of the mixture.

(b) *Potentiometrically.* The method described previously (Part I, *loc. cit.*) was used on a sample (40·97 mg.): 100 g. of starch combined with 3·70 g. of iodine, corresponding to an amylose content of 19·0%.

Methylation of Maple Starch.—The specimen (4 g.) was dispersed in water (30 c.c.) and to the rapidly stirred suspension, in an atmosphere of nitrogen at room temperature, sodium hydroxide (14 c.c.; 30%) was added during 2 hours. With continued stirring, further alkali (50 c.c.) was added dropwise simultaneously with methyl sulphate (28 c.c.) in portions of 10, 10, and 8 c.c., at intervals of 20 minutes between each addition. Acetone (20 c.c.) was then added and the methylation procedure repeated with sodium hydroxide (70 c.c.) and methyl sulphate (28 c.c.). Acetone (100 c.c.) was added and the whole was mixed. Acetone was then removed by distillation but a satisfactory separation of the methylated starch was not obtained. The mixture was therefore cautiously neutralised with sulphuric acid and dialysed. One-quarter of this material was concentrated to a small volume and subjected to twelve more methylations. The product, isolated in the usual way (Part I, *loc. cit.*), was a greenish material (1·01 g.), soluble in acetone and chloroform and having $[\eta]_{sp.}^{20}$ 1·4 (*c*, 0·40 in *m*-cresol) corresponding to a molecular weight of 436 000 for the unmethylated starch ($Km = 1·3 \times 10^{-4}$) (Hirst and Young, *J.*, 1939, 1471) (Found: OMe, 43·5%).

The methylated product was fractionated by successive extractions under reflux with mixtures (50 c.c.) of light petroleum (b. p. 60—80°) and chloroform in the following proportions: 95 : 5, 90 : 10, 85 : 15, and 80 : 20. The product dissolved almost completely in the 85 : 15 solvent mixture and the fraction obtained (0·96 g.) was unchanged in methoxyl content and viscosity.

At a later stage, when the presence of a methylated pentose was detected in the hydrolysate of the methylated starch, another fractionation was attempted with the object of removing the methylated pentosan. The methylated starch (0·70 g.) was dissolved in chloroform (15 c.c.), and light petroleum added until the solution became turbid. 0·45 g. of material was precipitated which was boiled with methanol (100 c.c.) and centrifuged. The undissolved material amounted to 0·15 g. and the methanol solution gave 0·30 g. of solid on evaporation. The light petroleum–chloroform solution gave 0·17 g. of product. A portion of each fraction was hydrolysed and examined on the paper chromatogram, but the spot due to the dimethyl pentose was present in all the fractions in approximately constant amount.

Hydrolysis of Methylated Maple Starch and Separation of the Methylated Glucoses.—The methylated starch (0·61 g.) was boiled with methanolic hydrogen chloride for 7 hours, and after removal of the methanol the mixture of glucosides was hydrolysed for 7 hours at 100° with

hydrochloric acid (1%). The acid was neutralised with silver carbonate, and the solution was filtered and treated with hydrogen sulphide. After filtration through " Filter Cel," the filtrate was deionized with " Amberlite " resins and after removal of solvent a colourless syrup (0·62 g.) was obtained. When the syrup was examined on the paper chromatogram (Hirst, Hough, and Jones, *J.*, 1949, 928) and sprayed with aniline oxalate, spots were obtained corresponding to tetramethyl glucopyranose (brown; $R_G = 1·00$), 2 : 3 : 6-trimethyl glucose (brown; R_G 0·85), 2 : 3-dimethyl xylose (pink; R_G 0·78), 2 : 3-dimethyl glucose (brown; R_G 0·65), and a trace of another dimethyl glucose (brown; R_G 0·59) and 2-methyl xylose (pink; R_G 0·50). The di-, tri-, and tetra-methyl glucose fractions were estimated quantitatively by hypoiodite oxidation in the usual way (Part I, *loc. cit.*) as follows :

Titration (*c.c. of* 0·0101N-$Na_2S_2O_3$)

	(1)	(2)	Difference		Mean
Blank	9·86	9·78	—	—	—
Dimethyl glucose	9·48	9·38	0·38	0·40	0·39
Trimethyl glucose	3·07	3·20	6·79	6·58	6·66
Tetramethyl glucose	9·63	9·54	0·23	0·24	0·235

This gives 3·2% of tetramethyl glucose, 91·4% of trimethyl glucose, and 5·4% of dimethyl glucose (expressed as glucose). After correction for the trimethyl glucose arising from amylose (19%) the proportion of end-group is 3·82% (as glucose), giving an average chain length of 26·2 glucose units. Expressed as wt.% of each methylated glucose (not corrected for amylose) the figures are tetramethyl glucopyranose 3·5%, trimethyl glucose 91·5%, and dimethyl glucose 5·0%.

Separation on a Cellulose Column.—The syrupy hydrolysate (0·61 g.) was added to a column of powdered cellulose (Hough, Jones, and Wadman, *J.*, 1949, 2511), and the column eluted with light petroleum (b. p. 100—120°)–butanol (60 : 40) saturated with water in the usual way. The eluate was collected in 7-c.c. fractions (rate, *ca.* 9 c.c./hour) after the first 100 c.c. of eluate which contained no sugars had been discarded.

Tubes 40—80 which contained the tetramethyl glucose fraction were combined and concentrated. After dissolution in water and treatment with charcoal a partly crystalline material was obtained which on extraction with boiling light petroleum (b. p. 40—60°) gave crystalline tetramethyl glucopyranose (17 mg., 3·3%), m. p. 88—92°, $[\alpha]_D$ +107° (*c*, 1·0 in water; 30 minutes after dissolution), +83·5° (17 hours, constant). The trimethyl glucose fraction (0·475 g., 92·9%) appeared in tubes 260—350. Three recrystallisations from dry ether gave m. p. 95—100°; the m. p. after recrystallisation from butyl acetate was 100—115°, and $[\alpha]_D^{15}$ +70° (*c*, 1·1 in water).

After 500 tubes, the solvent was changed to a 50 : 50 mixture of light petroleum–butanol saturated with water. Dimethyl glucose (19 mg., 3·8%) was collected in tubes 670—770 and had $[\alpha]_D$ +58·5° (*c*, 1·0 in water).

Thanks are expressed to Professor E. L. Hirst, F.R.S., for his interest, to the National Heart Institute, Washington, D.C., for the award of a Public Health Research Fellowship (to C. E. B.), to Mr. W. G. Campbell, Forest Products Research Laboratory for the maple starch, and to Imperial Chemical Industries Limited and the Distillers Company Limited for grants.

KING'S BUILDINGS, UNIVERSITY OF EDINBURGH. [*Received, November 13th*, 1951.]

188. *Synthetic Long-chain Aliphatic Compounds. Part IX.* Some Antituberculous Long-chain Amines.*

By D. E. Ames and R. E. Bowman.

(*With a Note by* G. A. H. Buttle and S. Squires.)

Several long-chain αω-tetramethyldiamines have been prepared by standard methods. The demonstration of antituberculous activity of 2-undecylpiperidines (Bowman and Fordham, *J.*, 1951, 2753) has led to a fuller examination of these bases, many of which have been prepared for biological test. All the isomeric *n*-dodecyl-piperidines and -pyrrolidines have also been made in an examination of the relation between structure and activity.†

Although long-chain primary αω-diamines and related compounds have been examined for antibacterial activity (King, Lourie, and Yorke, *Ann. Trop. Med. Parasit.*, 1938, **32**, 177; Fuller, *Biochem. J.*, 1942, **36**, 548), the corresponding αω-bisdimethylamines (I) have, so far as we are aware, escaped attention.

In the first instance, we examined the decamethylene compounds. Since decamethylenediamine and the di-*tert.*-amine (I; $n = 10$) were available from other work, it was only necessary to prepare the remaining bismethylamine (II) which was obtained from decamethylene dibromide as follows:

$$Me_2N\cdot[CH_2]_n\cdot NMe_2 \quad (I)$$

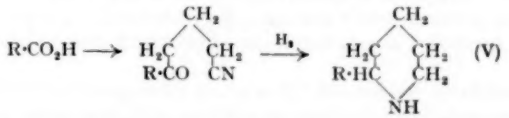
$$Br\cdot[CH_2]_{10}\cdot Br \longrightarrow CH_2Ph\cdot NMe\cdot[CH_2]_{10}\cdot NMe\cdot CH_2Ph \xrightarrow{H_2\text{–}Pd} NHMe\cdot[CH_2]_{10}\cdot NHMe \quad (II)$$

Next we prepared the di-*tert.*-amines (I; $n = 16$ and 18) by standard methods starting from hexadecane-1 : 16-dicarboxylic acid. Preliminary tests *in vitro* showed that, while the decamethylene derivatives were not particularly active, the compounds (I; $n = 16$ and 18) possessed considerable bacteriostatic activity against a number of micro-organisms including *Staphylococcus aureus* and *Mycobacterium tuberculosis*, the higher member being the more active. Two further amines (I; $n = 22$) and (III), the latter being prepared as indicated, were equally active.

$$CO_2H\cdot[CH_2]_{16}\cdot CO_2H \longrightarrow CH_3\cdot CO\cdot[CH_2]_{16}\cdot CO\cdot CH_3 \xrightarrow{Me_2NH\text{–}H_2} Me_2N\cdot CHMe\cdot[CH_2]_{16}\cdot CHMe\cdot NMe_2 \quad (III)$$

On the other hand, replacement of carbon atoms in the chain as in (IV) led to inactive material; the base was readily prepared by cyanoethylation of decamethylene glycol (Bruson and Riener, *J. Amer. Chem. Soc.*, 1943, **65**, 23) followed by reduction and subsequent methylation of the resulting amine.

$$Me_2N\cdot[CH_2]_3\cdot O\cdot[CH_2]_{10}\cdot O\cdot[CH_2]_3\cdot NMe_2 \quad (IV)$$



(V)

However, owing to the high toxicity of the active compounds attention was directed to other classes of long-chain bases. At this time, 2-undecylpiperidine (V; $R = C_{11}H_{23}$) had been prepared in this laboratory (Bowman and Fordham, *loc. cit.*) by the route outlined above and was examined for antibacterial properties. Tests against *M. tuberculosis in vitro* revealed that, although somewhat less active than the straight-chain amines, it was much less toxic, and accordingly we prepared a series of long-chain-substituted piperidines and some related pyrrolidines.

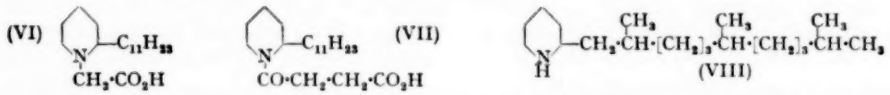
* Part VIII, *J.*, 1952, 677.

† Since this manuscript was prepared an announcement of similar work by Barry and his colleagues has appeared (*Nature*, 1951, **168**, 539).

The amine (V; R = $C_{11}H_{23}$) was first used for the preparation of several derivatives. Thus, 1-methyl-2-undecylpiperidine was obtained by methylation and was converted into the hydrochloride and methiodide. An impure sample of the carboxylic acid (VI) was prepared by condensation with ethyl chloroacetate and subsequent hydrolysis, and the amic acid (VII) was obtained, as an oil, by reaction with succinic anhydride.

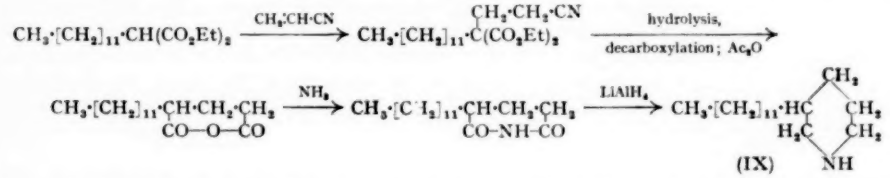
A series of 2-alkylpiperidines was then prepared, first, from the δ-keto-cyanides, and, secondly, by catalytic hydrogenation of the corresponding alkylpyridines. Satisfactory yields of 2-alkylpyridines were conveniently obtained by condensation of 2-picolyl-lithium with alkyl bromides (cf. Ziegler and Zeiser, *Annalen*, 1931, **485**, 179; for a review see Barkovsky, *Ann. Chim.*, 1944, **19**, 487). The maximum antibacterial activity in compounds (V) appeared to occur when the alkyl chain consisted of 12—15 carbon atoms.

The keto-cyanide method was also applied to the synthesis of the branched-chain amine (VIII), an oil, which furnished a hydrochloride of indefinite melting point, presumably



containing most or all of the possible isomers. Repeated recrystallisation of this material yielded a product of sharp melting point, which appeared to be a single isomer. This product had antituberculous activity similar to that of the straight-chain compounds.

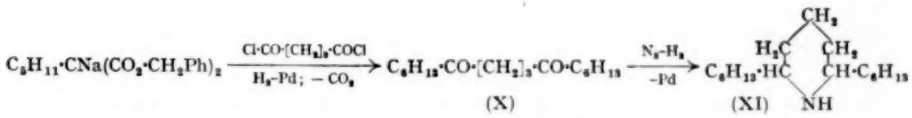
1-Dodecylpiperidine was readily obtained by hydrogenation of dodecylpyridinium bromide at normal temperature and pressure over Raney nickel W7 catalyst (Adkins and Billica, *J. Amer. Chem. Soc.*, 1948, **70**, 698) in the presence of diethylamine (cf. Barltrop and Taylor, *J.*, 1951, 108). 3-Dodecylpiperidine (IX) was prepared as in the annexed scheme. An analogous method for the synthesis of 4-dodecylpiperidine began by reduction


$CH_3 \cdot [CH_2]_{11} \cdot CH(CO_2Et)_2$
$CH_2 \cdot CH \cdot CN$
$CH_3 \cdot [CH_2]_{11} \cdot C(CH_2 \cdot CH_2 \cdot CN)(CO_2Et)_2$
hydrolysis, decarboxylation; Ac_2O
$CH_3 \cdot [CH_2]_{11} \cdot CH \cdot CH_2 \cdot CH_2$ (CO—O—CO)
NH_3
$CH_3 \cdot [CH_2]_{11} \cdot CH \cdot CH_2 \cdot CH_2$ (CO–NH–CO)
$LiAlH_4$
$CH_3 \cdot [CH_2]_{11} \cdot HC$ CH_2 H_2C CH_2 NH
CH_2
(IX)

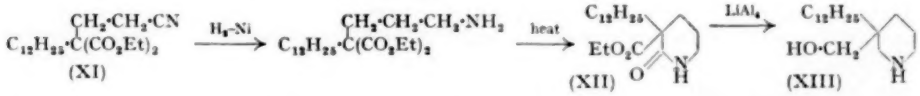
of ethyl dodecylmalonate with lithium aluminium hydride to 2-dodecylpropane-1 : 3-diol; however, repeated attempts to prepare the dibromide therefrom failed, and this route was abandoned. Reaction of 4-picolyl-lithium with dodecyl bromide yielded a complex mixture from which the required product could not be isolated. The alkylation of 4-picoline with undecyl chloride in the presence of sodamide, as described by Knight and Shaw (*loc. cit.*) and Barkovsky (*loc. cit.*), was readily effected, however. An attempt to hydrogenate the resulting 4-dodecylpyridine at normal pressure over Raney nickel W7 catalyst (as employed in the case of 2-alkylpyridines) was unsuccessful, but reduction with sodium and ethanol furnished 4-*n*-dodecylpiperidine which was isolated as its crystalline hydrochloride.

To examine the effect of the introduction of an alkyl group at each of the α-positions of piperidine, the synthesis of 2 : 6-dihexylpiperidine (XI) was investigated; such amines appeared to be accessible by reduction of 1 : 5-diketones in the presence of ammonia. The debenzylation ketone synthesis (Bowman, *J.*, 1950, 325) provides two possible methods for the synthesis of symmetrical 1 : 5-diketones: first, condensation of an acid chloride with an alkylidenedimalonic ester and, secondly, condensation of glutaroyl dichloride with an alkylmalonic ester. Both methods were examined, but the former was unsuccessful as the attempted ester interchange between ethyl propylidenedimalonate and benzyl alcohol in the presence of sodium ethoxide evidently resulted in a retrograde Michael reaction (cf. Ingold and Powell, *J.*, 1921, **119**, 1976). Condensation of glutaroyl chloride with dibenzyl sodio-amylmalonate did, however, furnish the diketone (X) in small yield (25%). Catalytic hydrogenation of this in the presence of ammonia gave a heterogeneous

product, from which 2 : 6-dihexylpiperidine (XI) was isolated as the crystalline hydrochloride.

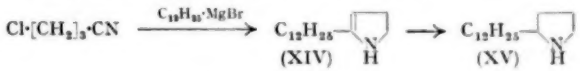


The synthesis of the 3 : 3-disubstituted piperidine (XIII), showing a further structural variation, was effected by the following route :

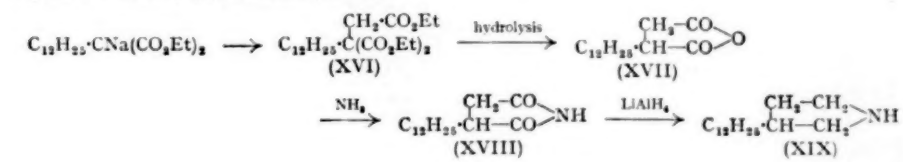


Catalytic hydrogenation of the acrylonitrile adduct (XI) of ethyl dodecylmalonate furnished the amine which, without isolation, was heated to give the carbethoxy-piperidone (XII). This was reduced with lithium aluminium hydride to 3-dodecyl-3-hydroxymethylpiperidine (XIII).

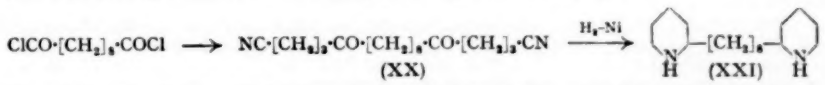
The three isomeric dodecylpyrrolidines were also prepared for comparison with the alkylpiperidines. 1-Dodecylpyrrolidine was obtained by alkylation of pyrrolidine by dodecyl bromide and anhydrous potassium carbonate. 2-Dodecylpyrrolidine (XV) appeared to be accessible from the alkylpyrroline (XIV). An impure sample of the latter was produced in small yield by reaction of dodecylmagnesium bromide with 3-chloropropyl cyanide, the method employed for the synthesis of shorter-chain compounds of this type by Craig, Bulbrook, and Hixon (*J. Amer. Chem. Soc.*, 1931, **53**, 1831). The alkylpyrroline could not be purified and the crude product was therefore hydrogenated, the resulting dodecylpyrrolidine being isolated as the crystalline hydrochloride. The



remaining isomer, 3-dodecylpyrrolidine, was prepared by a route analogous to that used for the synthesis of 3-dodecylpiperidine. Thus, ethyl sodiododecylmalonate was alkylated with ethyl chloroacetate and the product (XVI) converted into the anhydride (XVII). The corresponding imide (XVIII) was reduced with lithium aluminium hydride to the required 3-dodecylpyrrolidine (XIX).

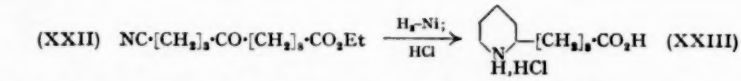


Finally, a base (XXI), incorporating both the long-chain αω-diamine and the α-alkylpiperidine structure, was synthesised. Use of sebacoyl chloride in the δ-keto-cyanide synthesis already mentioned gave a 33% yield of the diketo-dicyanide (XX), which was catalytically hydrogenated to 1 : 8-di-2′-piperidinyloctane (XXI) :



The acidic compounds separated during the isolation of (XX) were esterified with ethanol and the resulting esters, on fractional distillation, furnished a small yield (15%) of slightly impure ethyl 13-cyano-10-ketotridecanoate (XXII) evidently formed from the sebacoyl chloride by incomplete reaction. Catalytic hydrogenation of this product, followed

by hydrolysis of the ester group, gave 2-8′-carboxyoctylpiperidine (XXIII) isolated as its hydrochloride.



(XXII) $NC\cdot[CH_2]_5\cdot CO\cdot[CH_2]_5\cdot CO_2Et$ —H_2-Ni; HCl→ $[CH_2]_8\cdot CO_2H$ (XXIII)

Biological Results [by G. A. H. BUTTLE and S. SQUIRES].—The compounds described in the preceding section have all been tested against *Staphylococcus aureus* and *Mycobacterium tuberculosis*, the results being set out in the annexed table. Inspection of them

	Maximum dilution inhibiting :[1] *Staph. pyogenes*[2]	*Myc. tuberculosis*[3]	Toxicity, L.D. 50, Subcut.; mg./kg.
Diamines			
$NH_2\cdot[CH_2]_{10}\cdot NH_2$	1/1000	—	—
$Me\cdot NH\cdot[CH_2]_{10}\cdot NHMe$	1/1000	Inactive	—
$Me_2N\cdot[CH_2]_{10}\cdot NMe_2$	1/1000	—	—
$Me_2N\cdot[CH_2]_{16}\cdot NMe_2$	$1/10^6$	1/512 000	5
$Me_2N\cdot[CH_2]_{18}\cdot NMe_2$	$1/2 \times 10^6$	1/512 000	5
$Me_2N\cdot[CH_2]_{22}\cdot NMe_2$	$1/2 \times 10^6$	$1/10^6$	5
$Me_2N\cdot CHMe\cdot[CH_2]_{14}\cdot CHMe\cdot NMe_2$	$1/10^6$	1/512 000	—
$(Me_2N\cdot[CH_2]_3\cdot O\cdot[CH_2]_6\cdot)_2$	1/1000	Inactive	—
(XXI)	1/4000	1/4000	—
2-R-1-R′-Piperidines			
R / R′			
C_6H_{13} / H	Inactive	1/4000	—
C_9H_{19} / H	1/32 000	1/128 000	—
$C_{11}H_{23}$ / H	$1/2 \times 10^6$	1/256 000	400
$C_{11}H_{23}$ / CH_3	$1/2 \times 10^6$	1/512 000	—
$C_{11}H_{23}$ / $CH_2\cdot CO_2H$	1/128 000	1/64 000	—
$C_{11}H_{23}$ / $CO\cdot CH_2\cdot CH_2\cdot CO_2H$	1/128 000	1/100 000	—
$C_{12}H_{25}$ / H	1/512 000	1/128 000	—
$C_{13}H_{27}$ / H	$1/10^6$	1/128 000	800
$C_{15}H_{31}$ / H	$1/2 \times 10^6$	1/256 000	250
$C_{17}H_{35}$ / H	1/800 000	1/256 000	400
$C_{19}H_{39}$ / H (VIII)	1×10^6	1/128 000	250
$[CH_2]_8\cdot CO_2H$ / H	Inactive	1/1000	—
Pyrrolidines			
1-$C_{12}H_{25}$	1/256 000	1/64 000	—
2-$C_{12}H_{25}$	$1/10^6$	1/128 000	—
3-$C_{12}H_{25}$	$1/10^6$	1/256 000	—
Pyridines			
2-$C_{12}H_{25}$	1/512 000	1/32 000	—
4-$C_{12}H_{25}$	$1/2 \times 10^6$	1/64 000	—
Piperidines			
1-$C_{12}H_{25}$	1/128 000	1/128 000	—
2-$C_{12}H_{25}$	1/512 000	1/128 000	—
3-$C_{12}H_{25}$	$1/10^6$	1/256 000	—
4-$C_{12}H_{25}$	$1/10^6$	1/512 000	—
Miscellaneous			
2 : 6-Di-*n*-hexylpiperidine	1/64 000	1/32 000	—
1-Dodecyl-1-methylpiperidinium bromide	1/256 000	1/128 000	25
1-Dodecylpyridinium bromide	$1/2 \times 10^6$	1/128 000	—
1 : 1-Dimethyl-2-undecylpiperidinium iodide	1/512 000	1/256 000	—
2-Heptadecyl-1 : 1-dimethylpiperidinium iodide	$1{\cdot}6 \times 10^6$	1/256 000	100
(XIII)	$1/2 \times 10^6$	1/512 000	100 *
Streptomycin	$1/10^6$	$1/10^6$	—

[1] In every instance half of the inhibitory concentration failed to prevent growth of test organism. [2] *Staphylococcus pyogenes*: N.C.T.C.6571; nutrient broth. [3] *Mycobacterium tuberculosis*: H.37 Rv.; Dubos medium.

* Intravenous, 25 mg./kg.; oral, 250 mg./kg. (no deaths).

suggests the following conclusions: (1) Maximum activity against both organisms in diamines (I) occurs when $n > 18$ and in piperidines (V) when $R > C_{11}$, and in both cases this activity is unaffected by branching of the chain. (2) The position of the chain in

the *n*-dodecyl-pyrrolidines and -piperidines has no marked effect on the activity against the *Staphylococcus* except in the case of the *tert.*-base where attachment of the alkyl substituent to the nitrogen atom lowers the activity; against *Myc. tuberculosis* the maximum activity is displayed in the isomer in which the long-chain is furthest from the nitrogen atom, *viz.*, 3-dodecylpyrrolidine and 4-dodecylpiperidine. (3) Although groupings containing the carboxylic acid function in the long-chain piperidines decrease the activity, introduction of a group containing a hydroxyl group (*e.g.*, XIII) is without effect and, indeed, it seems that future work in this direction with a view to a reduction of the toxicity of these compounds would be well worth while.

Tests were carried out *in vivo* with *n*-tridecylpiperidine but the results were disappointing: oral administration of 20 mg. daily to mice infected intravenously with *Myc. murine* (N.C.T.C. 5676) afforded no protection. [*Added*, 30.1.52]: Further tests made by Mr. S. R. M. Bushby revealed that after oral administration of 20 mg. of this substance the blood of mice showed no tuberculostatic activity and, although significant activity was found after the same dose given intraperitoneally, the compound proved too toxic, parentally for therapeutic use.

Experimental

General Procedures.—δ-Keto-cyanides (Bowman and Fordham, *loc. cit.*). The freshly distilled acid chloride (1·0 mol.) was added to a benzene solution of dibenzyl sodio-2-cyanoethylmalonate (1·05 mols.). The product was isolated in the usual manner, and hydrogenated in ethyl methyl ketone on palladised strontium carbonate (10% of Pd). Partial decarboxylation often interfered and was overcome by occasional evacuation and subsequent refilling with hydrogen. The solution was then boiled to complete decarboxylation, filtered, and evaporated, finally *in vacuo*. Acids were removed by washing the solution of the crude product in light petroleum (b. p. 60—80°)–ethyl acetate with excess of 0·1—0·5N-sodium hydroxide and then water. Evaporation of the dried ($MgSO_4$) solution furnished the keto-cyanide, which was purified by distillation or recrystallisation.

2-Alkylpyridines. An ethereal solution of ω-lithiopicoline (1·0 mol.) was prepared by Walter's method (*Org. Synth.*, 1934, **23**, 83); alkyl bromide (0·85 mol.) was then added and the stirred solution was refluxed for 3 hours. After addition of dilute potassium hydroxide solution, the separated aqueous layer was extracted with light petroleum (b. p. 60—80°) and the combined organic layers were washed with water, dried ($MgSO_4$), and fractionally distilled. Unchanged alkyl bromide was rejected and the 2-alkylpyridine collected.

2-Alkylpiperidines. The δ-keto-cyanide (Method A) or 2-alkylpyridine (Method B) in ethanol was hydrogenated on Raney nickel W7 catalyst (Adkins and Billica, *loc. cit.*). Evaporation of the filtered solution furnished a gelatinous residue, apparently containing aluminium hydroxide. The product was isolated by distillation *in vacuo* or by addition of dilute sodium hydroxide solution followed by extraction with light petroleum (b. p. 60—80°).

1 : 10-Bismethylaminodecane Dihydrochloride.—A mixture of decamethylene dibromide (10 g.) and benzylmethylamine (30 g.) was heated at 110° for 6 hours, then cooled to room temperature and diluted with anhydrous ether (100 ml.). After removal of benzylmethylamine hydrobromide (14 g.), the filtrate was distilled, giving 1 : 10-*bisbenzylmethylaminodecane* as a viscous oil, b. p. 210°/0·2 mm. (11 g.) (Found: N, 6·8. $C_{36}H_{60}N_2$ requires N, 7·4%).

A solution of this in ethanol (150 ml.) was hydrogenated at normal pressure over 10% palladised charcoal (3 g.) until hydrogen uptake ceased (2 mols.). After removal of catalyst, the filtrate was made acid by addition of concentrated hydrochloric acid (10 ml.) and evaporated to dryness on the steam-bath. Crystallisation of the residue from ethanol (100 ml.) gave the *dihydrochloride* as prisms, m. p. 258° (Found: N, 9·9. $C_{12}H_{30}N_2Cl_2$ requires N, 10·3%); by concentration of the mother-liquors, more product was obtained (total yield, 6·5 g.).

1 : 16-Diaminohexadecane Dihydrochloride.—A mixture of hexadecane-1 : 16-dicarboxylic acid (4 g.), chloroform (200 ml.), and concentrated sulphuric acid (50 ml.) was heated to 50° with stirring, and sodium azide (5 g.) added during 2 hours. After a further 2 hours' stirring at the same temperature, the lower acid layer was separated and poured into water. The resulting suspension of base sulphate was treated with excess of sodium hydroxide (10N) at the b. p. until all solid had disappeared; the cooled solution was extracted with chloroform. Evaporation of the organic extract furnished the crude diamine which was isolated as its *dihydrochloride* (2·5 g.), needles (from ethanol), m. p. 340° (decomp.) (Found: N, 8·5. $C_{16}H_{38}N_2Cl_2$ requires N, 8·5%).

1 : 16-*Bisdimethylaminohexadecane Dihydrochloride.*—Sodium hydrogen carbonate (1·15 g.) was added in portions to formic acid (5 ml.; 98%) followed by the foregoing amine dihydrochloride (2·0 g.) and formaldehyde (3 ml. of 40%), and the mixture was heated under reflux in an oil-bath at 105° for 16 hours. The solution was evaporated to dryness and the residue dissolved in water and basified with sodium hydroxide solution. The base was isolated with benzene and, after removal of solvent, was converted directly into its *dihydrochloride* which separated from *n*-amyl alcohol (10 ml.)–ethyl methyl ketone (20 ml.) in thin plates, m. p. 234° (Found : N, 7·1. $C_{20}H_{46}N_2Cl_2$ requires N, 7·3%).

1 : 18-*Bisdimethylamino-octadecane Dihydrochloride.*—(*a*) Octadecamethylene-1 : 18-diamine (Pfeiffer and Lübbe, *J. pr. Chem.*, 1933, **136**, 321) was methylated as in the previous experiment, furnishing the *dihydrochloride* as clusters of plates (from *n*-propanol–ethyl methyl ketone), m. p. 234° (Found : N, 6·6; Cl, 17·6. $C_{22}H_{50}N_2Cl_2$ requires N, 6·8; Cl, 17·2%).

(*b*) Hexadecane-1 : 16-dicarboxylic acid (2·0 g.) was warmed at 50° with thionyl chloride (10 c.c.) for 2 hours and, after removal of the excess of thionyl halide, the acid chloride was dissolved in ether (50 c.c.). This solution was gradually added to an ethereal solution of dimethylamine (40 c.c.; 2M), and the mixture refluxed for 30 minutes and then evaporated *in vacuo*. The residual product was washed with potassium hydrogen carbonate solution and water; crystallisation from ethyl acetate–light petroleum (b. p. 60—80°) (activated charcoal) furnished *NNN'N'-tetramethylhexadecane*-1 : 16-*dicarboxyamide* (1·3 g.) in large, lustrous plates, m. p. 98° (Found : N, 7·8. $C_{22}H_{44}O_2N_2$ requires N, 7·6%). This (0·95 g.) was added to a stirred solution of lithium aluminium hydride (0·2 g.) in ether (20 c.c.), and the mixture was boiled under reflux for 2 hours, the product being isolated with ethyl acetate in the usual manner. The resulting crude amine was treated with ethanolic hydrogen chloride to give the required dihydrochloride, m. p. 234—235° (0·8 g.).

1 : 22-*Bisdimethylaminodocosane Dihydrochloride.*—1 : 22-Dimethoxy-*n*-docosane (4·2 g.; m. p. 54°; obtained, as will be reported later, as a by-product during the preparation of 11-methoxyundecylmagnesium bromide), was dissolved in hydrogen bromide–acetic acid (50 ml.; 15% w/v), and concentrated sulphuric acid (7 ml.) was added. After being heated at 100° for 8 hours, the cooled mixture was poured into water, and the solid product (m. p. 56—60°) collected. After a further similar treatment with the same reagents, the crude 1 : 22-dibromodocosane had m. p. 68—70° and then crystallised from ethanol–ethyl acetate in plates, m. p. 71—71·5° (2·5 g.) (Signer and Sprecher, *Helv. Chim. Acta*, 1947, **30**, 1001, reported m. p. 71·5—72°). A solution in ethanolic dimethylamine (20 ml.; 30%) was set aside at room temperature for 10 days and then heated to 95° for 10 hours. The crude diamine obtained by evaporation of solvent was converted, in the usual manner, into its *dihydrochloride*, short prisms, m. p. 236°, from ethanol–ethyl methyl ketone (Found : N, 5·8. $C_{26}H_{58}N_2Cl_2$ requires N, 6·0%).

n-*Eicosane*-2 : 18-*dione.*—Hexadecane-1 : 16-dicarboxylic acid (10·5 g.) was converted into its dichloride with thionyl chloride (12 ml.) at 80° for 1 hour and volatile halides were removed under reduced pressure. The residue in benzene (50 ml.) was treated with ethoxymagnesiomalonic ester (0·15 mol.) and the product hydrolysed with propionic acid following the general instructions of Bowman (*J.*, 1950, 322), to give the *ketone* (crude yield, 7 g. after appreciable loss by accident), colourless prismatic needles (from ethyl acetate), m. p. 90·5—91° (Found : C, 77·4; H, 12·4. $C_{20}H_{38}O_2$ requires C, 77·2; H, 12·3%).

2 : 18-*Bisdimethylaminoeicosane Dihydrochloride.*—The foregoing ketone (3 g.) was hydrogenated at 45°/1 atm. in ethanol (130 ml.) containing dimethylamine (5 g.) over 5% palladised charcoal (2 g.) until absorption of gas was complete (2 mols.). After removal of catalyst, the filtrate was evaporated to dryness and the base isolated as its *dihydrochloride* (3·0 g.), tiny prisms (from ethanol–ethyl methyl ketone), m. p. 196° (Found : N, 6·5. $C_{24}H_{54}N_2Cl_2$ requires N, 6·4%).

1 : 10-*Di-2'-cyanoethoxydecane.*—Acrylonitrile (6·5 g.) was gradually added to a stirred mixture of decane-1 : 10-diol (10 g.), dioxan (30 c.c.; distilled over sodium), and potassium hydroxide solution (0·4 c.c.; 40%) at 25—30° (cf. Bruson and Riener, *loc. cit.*). The mixture was stirred for 6 hours, left overnight, then poured into dilute sulphuric acid, the product being isolated with ethyl acetate. Distillation yielded a material, b. p. 120—180°/0·1 mm.; which appeared to consist mainly of the mono-adduct, and then 1 : 10-di-2'-cyanoethoxydecane, b. p. 180—185°/0·1 mm., as a colourless oil (8 g.), which crystallised in clusters of prisms, f. p. 39—38° (thermometer in liquid). Reaction of the low-boiling material with acrylonitrile in the same manner yielded more product (4 g.; total yield, 75%).

1 : 10-*Di-3'-aminopropoxydecane.*—The foregoing dicyanide (12 g.) in ethanol (200 c.c.) was mixed with saturated ethanolic ammonia (100 c.c.) and hydrogenated on Raney nickel (W7) catalyst; absorption ceased when 3·9 l. had been taken up (calc., 3·8 l.). Distillation of the

filtered solution yielded material, b. p. 160—180°/0·2 mm., redistillation of which furnished **1 : 10-*di*-3′-*aminopropoxydecane*** (9 g.) as a colourless oil, b. p. 160—163°/0·3 mm., which crystallised in clusters of prisms, f. p. 28—27° (Found: C, 66·7; H, 12·8. $C_{16}H_{36}O_2N_2$ requires C, 66·6; H, 12·6%). The derived *dihydrochloride* crystallised from ethanol–ethyl methyl ketone in plates, m. p. 205—206° (Found: Cl, 20·0. $C_{16}H_{38}O_2N_2Cl_2$ requires Cl, 19·6%).

1 : 10-*Di*-3′-*dimethylaminopropoxydecane.*—A mixture of the foregoing amine (7·5 g.), formic acid (25 c.c.; 98%), and aqueous formaldehyde (25 c.c.; 35%) was heated at 100° for 12 hours and then poured into excess of sodium hydroxide solution, the product being isolated with light petroleum (b. p. 60—80°). **1 : 10-*Di*-3′-*dimethylaminopropoxydecane*** (7·5 g.) was distilled as a colourless oil, b. p. 157°/0·2 mm., n_D^{20} 1·4522 (Found: C, 69·8; H, 12·8. $C_{20}H_{44}O_2N_2$ requires C, 69·7; H, 12·9%). The *dihydrochloride* crystallised from ethyl methyl ketone–ethanol in plates, m. p. 176° (Found: Cl, 17·4. $C_{20}H_{46}O_2N_2Cl_2$ requires C, 17·0%).

δ-*Keto-cyanides.*—The general procedure was used for the preparation of the **δ-*keto-cyanides*** tabulated.

Keto-cyanides, R·CO·CH_2·CH_2·CH_2·CN.

R	Yield, %		Formula	Found C, %	Found H, %	Required C, %	Required H, %
n-Hexyl	68	n_D^{20} 1·4519, b. p. 100—105°/0·1 mm.	$C_{11}H_{19}ON$	73·0	10·2	72·9	10·6
n-Nonyl	80	n_D^{20} 1·4510, b. p. 138—140°/0·5 mm.	$C_{14}H_{25}ON$	74·8	10·6	75·3	11·3
n-Tridecyl	75	Thin plates, m. p. 44°, from methanol; b. p. 160—165°/0·4 mm.	$C_{16}H_{33}ON$	77·4	11·9	77·4	11·9
n-Heptadecyl	85	Lustrous rectangular plates, m. p. 60—60·5°, from methanol	$C_{22}H_{41}ON$	(N, 4·4%)		(N, 4·2%)	
2 : 6 : 10-Trimethylundecyl [1]	70	n_D^{20} 1·4570, b. p. 165—170°/0·5 mm.	$C_{19}H_{39}ON$	77·5	11·2	77·8	12·0

[1] Prepared from 3 : 7 : 11-trimethyldodecanoyl chloride (Karrer, Favarger, Merz, and Milhaud, *Helv. Chim. Acta*, 1948, **31**, 1505).

These cyanides were characterised by hydrolysis with ethanolic potassium hydroxide to the tabulated **δ-*keto-acids.***

Keto-acids, R·CO·CH_2·CH_2·CH_2·CO_2H.

R		Found Formula	Found C, %	Found H, %	Found Equiv.	Required C, %	Required H, %	Required Equiv.
n-Hexyl	Lustrous plates,[1,2] m. p. 60—61°	—	—	—	—	—	—	—
n-Nonyl	Plates,[1] m. p. 80—81°	$C_{14}H_{26}O_3$	70·0	10·7	—	69·4	10·8	—
n-Tridecyl	Plates,[3,4] m. p. 91—92°	$C_{18}H_{34}O_3$	72·2	11·4	301	72·4	11·5	298
n-Heptadecyl	Plates,[3] m. p. 98—99°	$C_{22}H_{42}O_3$	74·6	11·4	352	74·5	11·9	355

[1] From ethyl acetate–light petroleum (b. p. 40—60°). [2] Franke *et al.* (*Monatsh.*, 1936, **69**, 167) gave m. p. 60°. [3] From methanol. [4] Hirata and Nakanishi (*Bull. Chem. Soc., Japan*, 1949, **22**, 121) give m. p. 81·5° which seems unexpectedly low.

2-*Alkylpyridines.*—The procedure already described gave 2-dodecyl- (67%), b. p. 122—124°/0·4 mm., n_D^{20} 1·4813 (Barkovsky, *loc. cit.*, gave n_D^{14} 1·4858), and 2-pentadecyl-pyridine (25%), b. p. 158—162°/0·5 mm., f. p. 25° (Knight and Shaw, *loc. cit.*, record m. p. 29°).

2-*Dodecylpyridine Hydrochloride.*—Hydrogen chloride was passed into a solution of the base in light petroleum (b. p. 60—80°). The crystalline product was placed in a vacuum-desiccator over potassium hydroxide to remove excess of hydrogen chloride. The *hydrochloride* separated from light petroleum (b. p. 60—80°)–ethyl methyl ketone in microscopic plates, m. p. 63—64° (Found: Cl, 12·3. $C_{17}H_{30}NCl$ requires Cl, 12·5%).

2-*Alkylpiperidines.*—Reduction of the appropriate δ-keto-cyanide (Method A) or alkylpyridine (Method B) furnished the ***amines*** (V), and the ***hydrochlorides*** tabulated.

2-Alkylpiperidines.

Alkyl	Prep. (yield, %)	B. p./mm.	n_D^{20}	Formula	Found C,%	Found H, %	Required C, %	Required H, %
n-Hexyl	A (70)	57°/0·4	1·4569	$C_{11}H_{23}N$	78·1	13·5	78·0	13·7
n-Nonyl	A (80)	95—98°/0·5	1·4611	$C_{14}H_{29}N$	79·8	13·5	79·5	13·8
n-Dodecyl	B (90)	133—135°/0·7 (f. p. 18—17°)	1·4626	$C_{17}H_{35}N$	80·9	14·0	80·5	13·9
n-Tridecyl	A (71)	135—138°/0·4 (f. p. 16—15°)	1·4630	$C_{18}H_{37}N$	81·2	13·8	80·8	13·9
n-Pentadecyl	B (83)	154—157°/0·4 (f. p. 26—25°)	1·4646	$C_{20}H_{41}N$	80·6	14·1	81·3	14·0
n-Heptadecyl	A (80)	170—172°/0·3 (f. p. 29°)	—	$C_{22}H_{45}N$	81·4	14·0	81·6	14·0
2 : 6 : 10-Trimethylundecyl	A (70)	125—128°/0·4	1·4638	$C_{19}H_{39}N$	81·1	13·6	81·1	14·0

2-Alkylpiperidine Hydrochlorides.

Alkyl		M. p.	Formula	Found: Cl, %	Required: Cl, %
n-Hexyl	Large prismatic needles [1]	159°	$C_{11}H_{24}NCl$	17·6	17·2
n-Nonyl	Needles [1]	140	$C_{14}H_{30}NCl$	14·7	14·3
n-Dodecyl	Fine needles [2]	154—155	$C_{17}H_{36}NCl$	12·4	12·2
n-Tridecyl	,,	138	$C_{18}H_{38}NCl$	12·2	11·7
n-Pentadecyl	,,	138—139	$C_{20}H_{42}NCl$	10·8	10·7
n-Heptadecyl	Fine needles [1]	136—137	$C_{22}H_{46}NCl$	10·3	9·8
2 : 6 : 10-Trimethyl-undecyl	Small plates [3]	145—146	$C_{16}H_{40}NCl$	11·0	11·2

[1] From methyl ethyl ketone–ethanol. [2] From ethanol. [3] Separated from the mixture of isomers of indefinite m. p. by repeated crystallisation from ethyl methyl ketone.

1-*Methyl*-2-*undecylpiperidine*.—A mixture of 2-undecylpiperidine (1·5 g.; Bowman and Fordham, *loc. cit.*), formic acid (1·5 c.c.; 98%), and aqueous formaldehyde (1·5 c.c.; 35%) was heated at 100° for 12 hours. After addition of excess of dilute sodium hydroxide solution, 1-*methyl*-2-*undecylpiperidine* was isolated with light petroleum (b. p. 60—80°) and distilled as a colourless oil, b. p. 120°/0·4 mm., n_D^{20} 1·4626 (1·2 g.) (Found: C, 80·7; H, 14·1. $C_{17}H_{35}N$ requires C, 80·6; H, 13·9%). The *hydrochloride* crystallised from ethyl methyl ketone–light petroleum (b. p. 60—80°) in tiny prisms, m. p. 115—116° (Found: Cl, 12·8. $C_{17}H_{36}NCl$ requires Cl, 12·2%). The *methiodide* separated from ethanol in tiny prisms, m. p. 188° (Found: I, 31·9. $C_{18}H_{38}NI$ requires I, 32·1%).

Ethyl 2-*Undecylpiperidinoacetate*.—2-Undecylpiperidine (2·5 g.), ethyl chloroacetate (1·8 g.), and anhydrous potassium carbonate (2 g.) were heated at 110—115° for 4 hours and the mixture was then diluted with water, the product being extracted with ethyl acetate. Distillation yielded the *ester* as a colourless oil, b. p. 145—148°/0·1 mm., n_D^{20} 1·4638 (2·1 g.) (Found: C, 73·7; H, 12·1. $C_{20}H_{39}O_2N$ requires C, 73·8; H, 12·1%).

The ester (2·0 g.) was refluxed with concentrated hydrochloric acid (15 c.c.) and water (15 c.c.) for 8 hours and the solution was then evaporated to dryness. The residue was stirred with ether, and aniline added dropwise until no further precipitation occurred. The filtered solution was evaporated to dryness giving a viscous oil, which only partly crystallised on storage. Attempts to purify this acid by crystallisation and by distillation were unsuccessful.

1 β-*Carboxypropionyl*-2-*undecylpiperidine*.—Succinic anhydride (0·6 g.) in benzene (15 c.c.) was refluxed with 2-undecylpiperidine (1·5 g.) for 15 minutes and the solution was then evaporated. The residual gum did not crystallise and was therefore dissolved in benzene (20 c.c.) and shaken with 0·5N-sodium hydroxide (50 c.c.). The separated aqueous layer was acidified and extracted repeatedly with benzene, the extracts being washed with water and evaporated. Removal of the last traces of solvent at 100°/0·5 mm. furnished 1-β-*carboxypropionyl*-2-*undecylpiperidine* as an almost colourless gum (Found: C, 70·4; H, 11·1. $C_{22}H_{41}O_3N$ requires C, 70·7; H, 11·0%).

2-*Heptadecyl*-1-*methylpiperidine*.—The foregoing amine (10 g.) was methylated by the same procedure as 2-undecylpiperidine. 2-*Heptadecyl*-1-*methylpiperidine* (8·5 g.) was distilled as a colourless oil, b. p. 166°/0·4 mm., which solidified on cooling and had f. p. 23° (thermometer in liquid) (Found: C, 82·2; H, 13·8. $C_{23}H_{47}N$ requires C, 81·8; H, 14·0%). The *hydrochloride* crystallised from ethyl methyl ketone–light petroleum (b. p. 60—80°) in colourless plates, m. p. 116—117° (Found: Cl, 9·7. $C_{23}H_{48}NCl$ requires Cl, 9·5%), and the *methiodide* from ethanol in microscopic plates, m. p. 218° (Found: I, 27·0. $C_{24}H_{50}NI$ requires I, 26·5%).

1-*Dodecylpyridinium Bromide*.—Dodecyl bromide (25 g.) was heated with pyridine (8 g.) at 150° for 1 hour and, on cooling, the mass crystallised. Recrystallisation from ethyl methyl ketone yielded large, colourless needles of 1-*dodecylpyridinium bromide monohydrate*, m. p. 74—75° (Found: C, 58·9; H, 9·1; Br, 22·9. $C_{17}H_{30}NBr,H_2O$ requires C, 58·9; H, 9·3; Br, 23·1%). Knight and Shaw (*J.*, 1938, 682) gave m. p. I, 89—90°, II, 125°, for the anhydrous substance. The water of crystallisation could not be removed *in vacuo* at 20° or 60°, and heating at 100°/0·5 mm. caused partial decomposition and some pyridine was produced. Addition of a solution of the hydrate in a minimum of ethanol to ether, as employed by Knight and Shaw, regenerated the unchanged hydrate.

1-*Dodecylpiperidine*.—The foregoing bromide (13 g.) in ethanol (150 c.c.) was hydrogenated at 20° and normal pressure in the presence of diethylamine (10 c.c.) and Raney nickel W7 catalyst (*ca.* 5 g.). Absorption was rapid (2·0 l. in 16 minutes) and eventually ceased when 2·6 l. had been taken up (calc., 2·7 l.). The filtered solution was evaporated and the residue dissolved in ethyl acetate; the solution was washed with 0·2N-sodium hydroxide solution and

then water, dried ($MgSO_4$), and distilled. 1-Dodecylpiperidine (8 g., 80%) was obtained as a colourless oil, b. p. 114—116°/0·4 mm., n_D^{20} 1·4578. Stross and Evans (*J. Amer. Chem. Soc.*, 1942, **64**, 2511) gave n_D^{20} 1·4588. The hydrochloride crystallised from ethyl methyl ketone in colourless needles, m. p. 187—188°. Karrer, Kahnt, Epstein, Jaffé, and Ishii (*Helv. Chim. Acta*, 1938, **21**, 223) reported m. p. 188—189°. The *methiodide* separated from light petroleum (b. p. 60—80°) in lustrous plates, m. p. 140° (Found: I, 31·6. $C_{18}H_{38}NI$ requires I, 32·1%).

α-*Dodecylglutaric Anhydride*.—Sodium (0·5 g.) was dissolved in ethyl dodecylmalonate (66 g., 0·2 mol.) at 100° and acrylonitrile (21 g., 0·4 mol.) was gradually added to the stirred mixture, which was then heated at 80—90° for 1 hour. After being heated under reflux with ethylene glycol (150 c.c.) and 10N-potassium hydroxide (100 c.c.) until evolution of ammonia ceased (12 hours), the solution was poured into 2N-sulphuric acid (750 c.c.), and the product isolated with ethyl acetate. Removal of the solvent yielded the crude triacid, which was decarboxylated at 200° (30 minutes); acetic anhydride (100 c.c.) was added and the mixture was refluxed for 2 hours and then distilled, to give the *anhydride* (37 g., 65%) as a colourless oil, b. p. 196—198°/0·5 mm., which rapidly crystallised and separated from light petroleum (b. p. 60—80°) in colourless plates, m. p. 57—58° (Found: C, 72·1; H, 10·6. $C_{17}H_{30}O_3$ requires C, 72·3; H, 10·7%).

A mixture of the anhydride (15 g.), aqueous ammonia (40 c.c.; *d* 0·88), and ethanol (10 c.c.) was distilled until the temperature reached 250° (bath) and kept at 240—250° for 20 minutes; on cooling, the product crystallised. α-*Dodecylglutarimide* (10 g., 65%) separated from light petroleum (b. p. 60—80°)–ethyl acetate (charcoal) in lustrous plates, m. p. 106—107° (Found: N, 5·3. $C_{17}H_{31}O_2N$ requires N, 5·0%).

3-*Dodecylpiperidine*.—The foregoing imide (6 g.) in a Soxhlet apparatus was extracted by refluxing a stirred solution of lithium aluminium hydride (3 g.) in ether (250 c.c.). After 4 hours' refluxing, N-potassium hydroxide (400 c.c.) was added and the product isolated with ethyl acetate. 3-*Dodecylpiperidine* (4 g.) distilled as a colourless oil, b. p. 136—138°/0·4 mm., n_D^{20} 1·4636 (Found: C, 81·0; H, 13·7. $C_{17}H_{35}N$ requires C, 80·5; H, 13·9%). The *hydrochloride* crystallised from ethyl methyl ketone–ethanol in clusters of prismatic needles, m. p. 137—138° (Found: Cl, 12·0. $C_{17}H_{36}NCl$ requires Cl, 12·2%).

2-*Dodecylpropane*-1 : 3-*diol*.—Ethyl dodecylmalonate (25 g.) was added during 30 minutes to a stirred solution of lithium aluminium hydride (6 g.) in ether (200 c.c.), and the mixture was then refluxed for 1 hour. The products were isolated with ether in the usual manner, distillation furnishing the *diol* as a colourless oil, b. p. 160—163°/0·5 mm., f. p. 69° (16·5 g., 89%), which separated from ethyl methyl ketone in lustrous, prismatic needles, m. p. 71—71·5° (Found: C, 73·7; H, 13·1. $C_{15}H_{32}O_2$ requires C, 73·7; H, 13·2%).

4-*Dodecylpyridine*.—4-Picoline (purified through the crystalline oxalate; Lidstone, *J.*, 1940, 241) was heated for 1 hour at 100° with powdered, commercial sodamide (5 g.); undecyl chloride (18 g.) was added and the mixture kept at 100° for 18 hours. After addition of water, the products were isolated with light petroleum (b. p. 60—80°) and fractionally distilled. 4-Dodecylpyridine (7 g.) was obtained as a colourless oil, b. p. 133—134°/0·3 mm., n_D^{20} 1·4834 (Barkovsky, *loc. cit.*, gave n_D^{14} 1·4856).

4-*Dodecylpiperidine Hydrochloride*.—Sodium (25 g.) was added in two portions to the foregoing amine (6 g.) in ethanol (100 c.c.); the mixture was then heated (bath, 120°) for 1 hour. More ethanol was added to dissolve the remaining sodium and, after removal of the alcohol by steam-distillation, the products were isolated with light petroleum (b. p. 60—80°). The crude product was dissolved in ethyl methyl ketone (40 c.c.), and concentrated hydrochloric acid (2 c.c.) added; a first crop (1·6 g.) of crystals separated at 20° and a second (1·3 g.) at 0°. Recrystallisation of the combined products from ethyl methyl ketone furnished fine needles of 4-*dodecylpiperidine hydrochloride*, m. p. 165° (Found: C, 69·9; H, 12·2; Cl, 12·4. $C_{17}H_{36}NCl$ requires C, 70·4; H, 12·5; Cl, 12·2%).

Attempted Synthesis of 12-*Ethyltricosane*-10 : 14-*dione*.—Propylidenemalonic ester (Cope, Hofmann, Wyckoff, and Hardenbergh, *J. Amer. Chem. Soc.*, 1941, **63**, 3452) was treated with ethyl sodiomalonate as described by Goss, Ingold, and Thorpe (*J.*, 1923, **123**, 3353). Ethyl 2-ethylpropane-1 : 1 : 3 : 3-tetracarboxylate, b. p. 150—160°/0·4 mm., was thus obtained in 61% yield.

This (60 g.), sodium (7·7 g.), and benzyl alcohol (72 g.) in benzene were subjected to ester-interchange in the usual manner, and decanoyl chloride (61 g.) was then added. The products were isolated and debenzylated by the general procedure, the resulting solution being boiled, filtered, and evaporated. Light petroleum (b. p. 60—80°; 300 c.c.) and water (800 c.c.) were

added to the residual oil and the mixture was basified with 2N-sodium hydroxide solution (160 c.c.). The aqueous layer was extracted with light petroleum, and the combined organic layers were washed with 0·5N-sodium hydroxide and then water, dried ($MgSO_4$), and evaporated. Repeated fractional distillation of the product yielded undecan-2-one, b. p. 57°/0·3 mm., f. p. 10° (thermometer in liquid), n_D^{20} 1·4319 (semicarbazone, m. p. 122—123°), and *benzyl decanoate*, b. p. 140—145°/0·2 mm., n_D^{20} 1·4909 (Found : C, 77·5; H, 10·3. $C_{17}H_{26}O_2$ requires C, 77·8; H, 10·0%).

Glutaroyl Dichloride.—A mixture of glutaric acid (50 g.) and thionyl chloride (80 c.c.) was kept at room temperature for 5 hours and then warmed at 50° for ½ hour. After removal of excess of thionyl chloride by distillation *in vacuo*, the dichloride (45 g.) was distilled as a colourless oil, b. p. 88°/5 mm.

Heptadecane-7 : 11-dione.—The sodio-benzyl ester (0·4 mol.), prepared in the usual manner from sodium (9·2 g.), benzyl alcohol (86·5 g.), and ethyl amylmalonate (92 g.) in benzene, was treated with glutaroyl dichloride (32 g., 0·19 mol.), and the product isolated, debenzylated, and decarboxylated according to the general procedure. The crude product was shaken with light petroleum (b. p. 60—80°; 300 c.c.), ethyl acetate (50 c.c.), and water (500 c.c.), and the mixture basified with N-sodium hydroxide (100 c.c.). The separated aqueous layer was extracted twice with ethyl acetate–light petroleum (b. p. 60—80°), and the combined organic layers were washed with 0·5N-sodium hydroxide solution (200 c.c.) and then water (three times), dried ($MgSO_4$), and evaporated under reduced pressure. Crystallisation of the residue from light petroleum (b. p. 60—80°)–ethyl acetate (activated charcoal) and then from methanol yielded colourless plates of *heptadecane-7 : 11-dione* (12·5 g., 25%), m. p. 80—81° (Found : C, 75·5; H, 11·9. $C_{17}H_{32}O_2$ requires C, 76·1; H, 12·0%).

2 : 6-Dihexylpiperidine Hydrochloride.—The foregoing diketone (8 g.) in ethanol (200 c.c.), and ethanol (50 c.c.) saturated with ammonia, was hydrogenated at 25° in the presence of palladised charcoal (1 g.; 5% of Pd) and palladised strontium carbonate (3 × 3 g.; 10% of Pd). Absorption ceased when 1 l. had been taken up (calc., 1·4 l.), and the filtered solution was distilled, to give the impure amine, b. p. 100—106°/0·3 mm., n_D^{20} 1·4702 (6 g.) (Found : C, 81·6; H, 12·6. Calc. for $C_{17}H_{35}N$: C, 80·6; H, 13·9%). Concentrated hydrochloric acid (3·5 c.c.) was added to a solution of the crude product in hot ethanol (50 c.c.), and *2 : 6-dihexylpiperidine hydrochloride* (2·2 g.), which separated on cooling, was recrystallised from ethanol, forming short rods, m. p. 147° (Found : C, 70·4; H, 12·5; Cl, 12·1. $C_{17}H_{36}NCl$ requires C, 70·4; H, 12·5; Cl, 12·2%). Evaporation of the mother-liquor furnished a viscous, brown oil, which was not investigated further.

Ethyl 2-Cyanoethyldodecylmalonate.—Sodium (0·2 g.) was dissolved in ethyl dodecylmalonate (26 g.) at 100° (1½ hours), and freshly distilled acrylonitrile (8 g.) was then added. After 1 hour's heating (bath, 110°), glacial acetic acid (3 g.) and water (200 c.c.) were added, the product being isolated with light petroleum (b. p. 40—60°). Ethyl 2-cyanoethyldodecylmalonate (20 g., 65%) distilled as a colourless oil, b. p. 198—203°/1 mm., n_D^{20} 1·4509.

Ethyl 3-Dodecyl-2-ketopiperidine-3-carboxylate.—The foregoing cyano-diester (3·3 g.) in ethanol was hydrogenated, on Raney nickel W7 catalyst, until absorption ceased. After evaporation of the filtered solution the residue was heated (bath, 150°) for 10 minutes and, on cooling, the product crystallised. The *ester* (2·2 g.) separated from light petroleum (b. p. 40—60°) in plates, m. p. 71—72° (Found : C, 71·2; H, 10·9. $C_{20}H_{37}O_3N$ requires C, 70·7; H, 11·0%).

In another experiment, an attempt was made to distil the crude reduction product; considerable decomposition resulted and only a small amount (15%) of a colourless oil, b. p. 205—210°/0·9 mm., was collected. This material rapidly solidified and recrystallisation from light petroleum (b. p. 40—60°) furnished fine needles of *3-dodecylpiperid-2-one*, m. p. 79—80° (Found : C, 76·4; H, 12·0. $C_{17}H_{33}ON$ requires C, 76·3; H, 12·4%). The latter was probably formed by partial hydrolysis of the ester by the alkali present in the catalyst and decarboxylation on distillation. A mixture of this product with the ester (m. p. 71—72°) melted at about 61°.

3-Dodecyl-3-hydroxymethylpiperidine.—The foregoing ester (1·3 g.) was added to a stirred solution of lithium aluminium hydride (1·5 g.) in ether (120 c.c.). After 2 hours' refluxing, 2N-sodium hydroxide (200 c.c.) was added and the product isolated with benzene. The resulting oil could not be induced to crystallise, nor could the derived hydrochloride, and the product was therefore distilled. *3-Dodecyl-3-hydroxymethylpiperidine* (0·6 g.) was obtained having b. p. 175—180°/0·5 mm., n_D^{20} 1·4793 (Found : C, 75·9; H, 12·7. $C_{18}H_{37}ON$ requires C, 76·3; H, 13·2%).

1 : 16-Dicyanohexadecane-4 : 13-dione.—Sebacoyl chloride (27·5 g., 0·115 mol.) was condensed

with dibenzyl sodio-2-cyanoethylmalonate (0·25 mol.) and the product debenzylated, decarboxylated, and isolated by the general procedure. Repeated crystallisation of the product from methanol furnished colourless plates of **1 : 16-*dicyanohexadecane*-4 : 13-*dione***, m. p. 72—73° (11 g., 33%) (Found : N, 9·2. $C_{18}H_{28}O_2N_2$ requires N, 9·2%). Hydrolysis with aqueous-ethanolic sodium hydroxide in the usual manner furnished **4 : 13-*diketohexadecane*-1 : 16-*dicarboxylic acid***, plates, m. p. 142—143°, from ethyl acetate (Found : C, 63·3; H, 9·0. $C_{18}H_{30}O_6$ requires C, 63·1; H, 8·8%).

This acid (5 g.) was reduced by the modified Wolff–Kishner method (Huang-Minlon, *J. Amer. Chem. Soc.*, 1946, **68**, 2487) with sodium hydroxide (5 g.) in water (5 c.c.), hydrazine hydrate (7 c.c.; 60%), and 2 : 2′-dihydroxydiethyl ether (80 c.c.). After the reaction mixture had been poured into excess of dilute sulphuric acid, the product was isolated with ethyl acetate, yielding hexadecane-1 : 16-dicarboxylic acid (3·8 g.), m. p. 123—124°, after crystallisation from ethanol.

1 : 8-*Di*-2′-*piperidyloctane*.—Hydrogenation of **1 : 16-dicyanohexadecane-4 : 13-dione** (7 g.), as previously, furnished a yellow oil (4·5 g.), b. p. 163—166°/0·3 mm., redistillation of which yielded the ***diamine***, b. p. 158—160°/0·2 mm., crystallising in prismatic needles, f. p. 37—36° (thermometer in liquid) (Found : C, 77·1; H, 12·3. $C_{18}H_{36}N_2$ requires C, 77·1; H, 12·9%). The derived ***dihydrochloride*** crystallised from ethanol–ethyl methyl ketone (charcoal) and then aqueous dioxan in microscopic plates, m. p. 229° (Found : Cl, 20·4. $C_{18}H_{38}N_2Cl_2$ requires Cl, 20·1%).

9-2′-*Piperidylnonanoic Acid Hydrochloride*.—The alkaline aqueous layer obtained during the synthesis of **1 : 16-dicyanohexadecane-4 : 13-dione** was acidified with sulphuric acid (20 c.c.; 20N), and the oily product taken up in ethyl acetate (100 c.c.). The organic layer was washed with water, dried ($MgSO_4$), and evaporated, the residue being esterified azeotropically with ethanol (80 c.c.), benzene (100 c.c.), and concentrated sulphuric acid (0·5 c.c.). Fractional distillation of the resulting esters furnished crude ***ethyl* 13-*cyano*-10-*ketotridecanoate***, b. p. 178°/0·2 mm., f. p. 41—40° (thermometer in liquid) (Found : C, 67·2; H, 9·5. $C_{16}H_{27}ON_3$ requires C, 68·3; H, 9·7%). This, without further purification, was hydrogenated, as before, and the resulting oily product was refluxed with concentrated hydrochloric acid (10 c.c.) and water (10 c.c.) for 8 hours. Evaporation of the solution and crystallisation of the residual solid from aqueous dioxan yielded plates of the ***amino-acid hydrochloride***, m. p. 170° (2·5 g.) (Found : N, 5·0. $C_{14}H_{28}O_2NCl$ requires N, 5·0%).

1-*Dodecylpyrrolidine*.—Dodecyl bromide (10 g.) and pyrrolidine (6 g.) were heated with anhydrous potassium carbonate (4 g.) at 100—110° for 2 hours and then at 150° for ½ hour. After addition of water, the product was isolated with ethyl acetate and distilled, b. p. 108—112°/0·5 mm. (8 g.). **1-*Dodecylpyrrolidine***, purified by regeneration from the crystalline hydrochloride, had b. p. 108—110°/0·4 mm., n_D^{20} 1·4559, f. p. −6° to −7° (Found : C, 80·8; H, 13·9. $C_{16}H_{33}N$ requires C, 80·3; H, 13·9%). The ***hydrochloride*** separated from chloroform–light petroleum (b. p. 60—80°) in microscopic plates, m. p. 159—160° (Found : Cl, 12·8. $C_{16}H_{34}NCl$ requires Cl, 12·9%).

2-*Dodecylpyrrolidine Hydrochloride*.—3-Chloropropyl cyanide (10 g.) was added to a stirred ethereal solution of the Grignard reagent prepared from magnesium (5·0 g.) and dodecyl bromide (50 g.). After the mixture had been refluxed for 2 hours, ammonium chloride solution (250 c.c.; 20%) was added and the separated aqueous layer was extracted with benzene. The combined organic layers were washed with 2N-sodium hydroxide and then water, dried (K_2CO_3), and evaporated. The fraction, b. p. 120—140°/0·2 mm. (14 g.), which was separated from higher- and lower-boiling products by fractional distillation, was evidently not homogeneous and partly crystallised. This crude product was hydrogenated in ethanol on Raney nickel W7 catalyst (1·3 l. absorbed). The filtered solution was evaporated and 0·5N-sodium hydroxide solution (250 c.c.) added to the residue, the oily product being taken up in light petroleum (b. p. 40—60°). The dried (K_2CO_3) petroleum solution was saturated with hydrogen chloride and then cooled at 0°. **2-*Dodecylpyrrolidine hydrochloride*** (1·1 g.), which separated, was recrystallised from light petroleum (b. p. 40—60°)–ethyl methyl ketone, forming lustrous plates, m. p. 83—84° (Found : C, 69·7; H, 12·3; Cl, 12·6. $C_{16}H_{34}NCl$ requires C, 69·7; H, 12·4; Cl, 12·9%).

***Dodecylsuccinic Anhydride*.**—Sodium (2·3 g.) was dissolved in ethanol (100 c.c.) and, after successive addition of ethyl dodecylmalonate (33 g.) and ethyl chloroacetate (16 g.), the mixture was refluxed for 5 hours. Diethylene glycol (150 c.c.) and 10N-potassium hydroxide (60 c.c.) were added, ethanol was removed by distillation, and the residue was refluxed for 5 hours and then poured into excess of dilute sulphuric acid. The crude tricarboxylic acid, isolated with

ethyl acetate, was decarboxylated at 210—220° (½ hour) and then refluxed with acetic anhydride (100 c.c.) for 2 hours. Distillation furnished dodecylsuccinic anhydride (14 g.), b. p. 172—175°/0·5 mm., which rapidly crystallised and separated from light petroleum (b. p. 60—80°) in fine needles, m. p. 71—72° (Barry and Twomey, *Proc. Roy. Irish Acad.*, 1947, **51**, *B*, 137, give m. p. 69—70·5°).

α-*Dodecylsuccinimide.*—The foregoing anhydride (8·2 g.) and aqueous ammonia (25 c.c.; *d* 0·88) were distilled until the bath-temp. reached 260° and then heated at 260° for ½ hour. α-*Dodecylsuccinimide*, which crystallised on cooling, was recrystallised from ethyl acetate–light petroleum (b. p. 60—80°) in microscopic plates, m. p. 94—95° (5·6 g.) (Found: C, 71·7; H, 10·5. $C_{16}H_{29}O_2N$ requires C, 71·8; H, 10·9%).

3-*Dodecylpyrrolidine.*—To a solution of lithium aluminium hydride (3 g.) in ether (100 c.c.) was added the foregoing imide (5·4 g.), and the mixture was stirred under reflux for 8 hours. Dilute potassium hydroxide solution was added and the product isolated with ethyl acetate; distillation yielded 3-*dodecylpyrrolidine* (2·4 g.) as a colourless oil, b. p. 134—138°/0·8 mm., n_D^{20} 1·4631 (Found: C, 80·4; H, 13·8. $C_{16}H_{33}N$ requires C, 80·3; H, 13·9%). The derived *hydrochloride* separated from light petroleum (b. p. 60—80°) in lustrous plates, m. p. 81° (Found: Cl, 12·4. $C_{16}H_{34}NCl$ requires Cl, 12·9%).

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189. *Studies in Light Absorption. Part X.* Further Observations on Ultra-violet Auxochromes. A Survey of the Effects of Some of the Less Common Elements.*

By K. Bowden and E. A. Braude.

The generalisations previously made (Part III, *J.*, 1946, 948) concerning the spectral effects of covalently saturated substituents on the ultra-violet light absorption of ethylenic and aromatic systems are amplified. Data are presented for 16 phenyl derivates $PhXR_n$ where X represents elements of Groups IV, V, VI, and VII of the Periodic Table and R = alkyl. When X = C, Si, Sn, Pb, or Halogen, the auxochromic effects are relatively small, whereas the elements of Groups V and VI produce large effects. Electronic interaction with the π-electron centre is particularly strong for the substituents NR_2, PR_2, SR, and SeR. These, and some connected observations on the effects of alkyl groups, are discussed in relation to current theories of electronic spectra.

In Part III (*loc. cit.*) a survey was presented of the data then available concerning the auxochromic effects of the commoner types of substituents when directly attached to ethylenic or benzenoid groups. It was shown that the bathochromic displacements due to a covalently saturated substituent X in a system C=C·X could be correlated (i) with the polarisability of the ethylenic group as conditioned by its molecular environment, and (ii) with the position of X in the Periodic Table. Thus, whereas alkyl, alkoxyl, and halogen substituents exert relatively small influences, the conjugating effect of amino and sulphide (thiol) substituents was even greater than that of simple, covalently unsaturated groups, such as a vinyl group; *e.g.*, the characteristic light-intensity absorption of vinylamines (C=C·NR_2) and vinyl sulphides (C=C·SR) lies at rather longer wave-lengths ($\lambda_{max.}$ near 2300 Å) than that of conjugated dienes (C=C·C=C; $\lambda_{max.}$ near 2200 Å). The influence of substituents such as NR_2 and SR is ascribed mainly to the interaction of their unshared *p*-electrons with the π-electrons of the adjacent double bond, and it was easily predictable that such interaction, which is conveniently termed π-*p* conjugation, would also be

* Part IX, *J.*, 1950, 379.

particularly large in the case of other Group V and VI elements, especially tervalent phosphorus derivatives.

During the last five years, many data have appeared in the literature bearing out the generalisations previously made and many additional examples of the effects of $-NR_2$ substituents (cf. Jones, Shen, and Whiting, *J.*, 1950, 236; Cocker, O'Meara, Schwarz, and Stuart, *ibid.*, p. 2052; Grob, *Helv. Chim. Acta*, 1950, **33**, 1787; Austin, Chanley, and Sobotka, *J. Amer. Chem. Soc.*, 1951, **73**, 5299), $-SR$ substituents (cf. Owen and Somade, *J.*, 1947, 1030; Owen and Sultanbawa, *J.*, 1949, 3109; Koch, *ibid.*, p. 387; Fehnel and Carmack, *J. Amer. Chem. Soc.*, 1949, **71**, 84; Ralls, Dodson, and Riegel, *ibid.*, p. 3320; Rosenkranz, Kaufmann, and Romo, *ibid.*, p. 3689; Price and Zomlefer, *ibid.*, 1950, **72**, 16; Nussbaum, Mancera, Rosenkranz, and Djerassi, *ibid.*, 1951, **73**, 3263), and halogen substituents (cf. Wood and Temin, *ibid.*, 1950, **72**, 139) in open-chain and cyclic ethylenic systems have been described. These, together with some additional data we have determined, make it possible to extend, and fill in several gaps in, the earlier survey of the commoner substituents (Table 1).

Our continuation of the work has been primarily directed towards a study of the less common auxochromes of Groups IV, V, and VI of the Periodic System. No systematic study of the light-absorption properties of organic compounds of the heavier elements has previously been made and the few scattered data available mostly refer to saturated derivatives. For the present purpose, the most suitable derivatives would be the sub-

TABLE 1. *Auxochromic effects in different ethylenic systems.* (*Bathochromic shifts in* Å *due to replacement of* H *by* X.)

X =	CR_3	NR_2	OR	SR	Cl	Br
X·C=C	50 [1]	400 [1]	—	450 [1]	50 [1]	—
X·C=C·C=C	50 [1]	650 [1]	—	280 [5]	60 [1]	100 [7]
X·Ph *	80 [2]	510 [2]	195 [2]	550 [2]	100 [2]	100 [2]
X·C=C·Ph	40 [3]	580 [3]	—	—	—	140 [3]
X·C=C·CO_2H	50 [4]	800 [1]	300 [1]	700 [6]	200 [1]	250 [1]
X·C=C·C=O	100 [1]	950 [1]	500 [1]	850 [1]	200 [1]	300 [1]

* Displacements of high-intensity *E*-band.

[1] Part III, *loc. cit.* [2] This paper (see Table 2). [3] From comparison of styrene and β-methylstyrene (cf. Braude and Timmons, *J.*, 1950, 2009), β-diethylaminostyrene and β-bromostyrene (see Experimental), respectively. [4] From comparison of crotonic and β-methylcrotonic acid (Braude and Timmons, unpublished). [5] From comparison of the enol ether and benzyl thioenol ether of cholest-4-en-3-one (Rosenkranz, Kaufmann, and Romo, *loc. cit.*). [6] From comparison of acrylic and β-benzylthioacrylic acid (Owen and Sultanbawa, *loc. cit.*). [7] From comparison of hexatriene and 3-bromohexatriene (Woods *et al.*, *J. Amer. Chem. Soc.*, 1948, **70**, 3394; 1950, **72**, 139).

stituted ethylenes of the type $R·CH{:}CH·XR_n$ where X is the key element and R is alkyl or hydrogen. However, as few such substances are known and as many of them are likely to be very unstable, the corresponding phenyl derivatives, $Ph·X·R_n$, which have been more fully investigated chemically, were chosen instead, the alkylated derivatives (R = Me or Et) being selected in preference to the parent hydrides (R = H) in view of their superior stability. The present communication deals with the near-ultra-violet absorption of sixteen such derivatives, in which X is C, Si, Sn, Pb, N, P, As, Sb, O, S, Se, Te, and Halogen, and some related compounds. Although the majority of these compounds are known, it became apparent in the early stages of the work that the preparative methods described are frequently unsatisfactory and yield products of doubtful purity. The derivatives of the Group V and VI elements, in particular, are very unstable in air and considerable effort was spent on devising satisfactory methods of preparation and manipulation, which are referred to in the experimental section.

The principal data are collected in Table 2 and Figs. 1—5. Amongst the compounds studied, earlier measurements were available only for dimethylaniline (Remington, *J. Amer. Chem. Soc.*, 1945, **67**, 1838; Klevens and Platt, *ibid.*, 1949, **71**, 1714), phenetole (Jacobs and Tuttle, *ibid.*, p. 1313), and the halogenobenzenes (Conrad-Billroth, *Z. physikal. Chem.*, 1932, *B*, 19, 76; Doub and Vandenbelt, *J. Amer. Chem. Soc.*, 1947, **69**, 2714), and, in these cases, the agreement between the earlier and present measurements is generally satisfactory. Benzene exhibits two main groups of bands in the near-ultra-violet region, one of moderately high intensity near 2000 Å (ε 8000) which will be referred to as the *E*-

band, and the other of low intensity near 2560 Å (ε 200) which will be referred to as the *B*-band.* A third very intense group of bands near 1800 Å (Platt and Klevens, *Chem. Reviews*, 1947, **41**, 301; Price and Walsh, *Proc. Roy. Soc.*, 1947, *A*, **191**, 22) lies outside the quartz-instrument range, and a fourth group, reported near 3400 Å, is of extremely low intensity (Sklar, *J. Chem. Physics*, 1937, **5**, 669; Lewis and Kasha, *J. Amer. Chem. Soc.*,

FIG. 1.

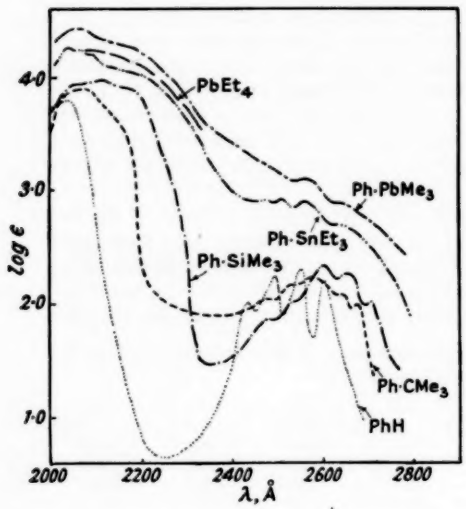


FIG. 3.

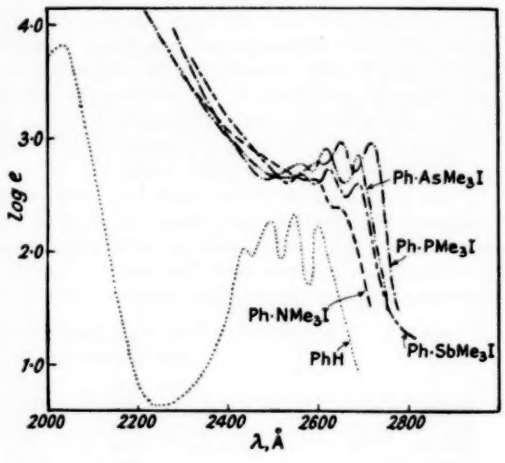
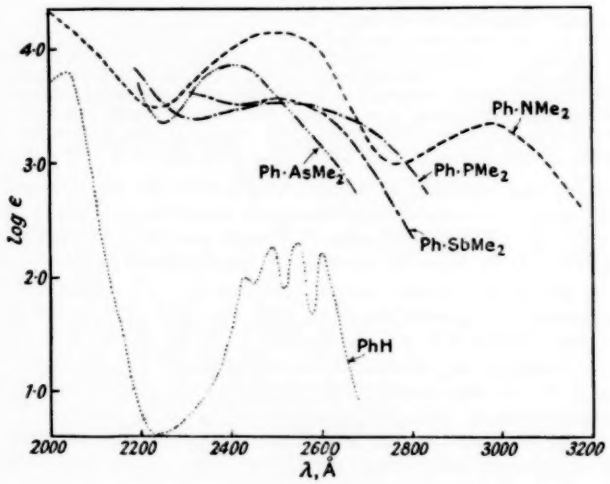


FIG. 2.



1945, **67**, 994). Substituents generally cause a bathochromic displacement and intensification of the *B*-band, as well as the appearance of a new band at longer wave-length than the *E*-band, but of similar intensity. The original *E*-band is just outside the present range of

* These designations were originally based (*Ann. Reports*, 1945, **42**, 105) on the qualitative theoretical interpretation of the bands, regarded as due to transitions of the ethylenic and benzenoid types. Fortunately, they are also indicative of the precise physical descriptions, since the most acceptable symmetry assignments of the excited states are E_{1u} and B_{2u}, respectively (Craig, *Discuss. Faraday Soc.*, 1950, **9**, 5; Burawoy, *ibid.*, p. 78).

measurements, but the vacuum-ultra-violet investigations of Price and Walsh (*loc. cit.*; *Discuss. Faraday Soc.*, 1950, **9**, 53) and Platt and Klevens (*loc. cit.*) and our own data (see Experimental) for methyl phenyl sulphide show that it is also retained in the substituted derivatives. The new high-intensity bands between 2000 and 2500 Å may be regarded as displaced *E*-bands, and the effects observed may be summarised in more detail as follows:

(i) The Group IV substituents CR_3, SiR_3, SnR_3, and PbR_3 cause only small bathochromic displacements which are largest with SiR_3. The substituents $SnEt_3$ and $PbMe_3$

FIG. 4.

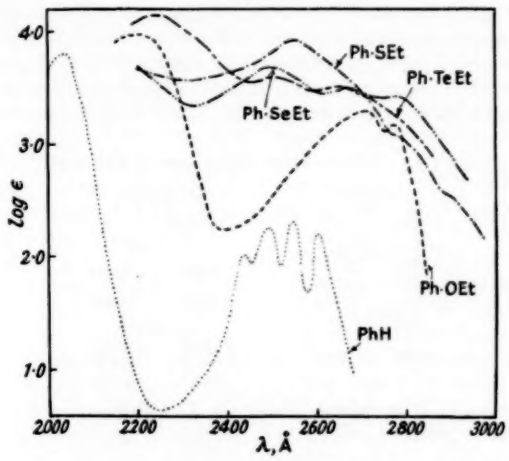
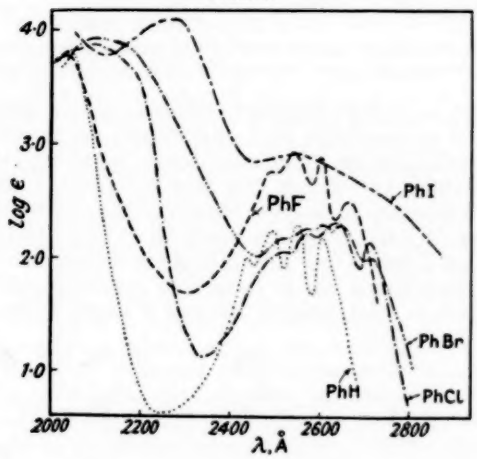


FIG. 5.



also cause pronounced increases in intensity, but these probably do not arise from interaction with the phenyl ring, but from the metallic groups themselves, since the corresponding tetra-alkyl derivatives also show intense continuous absorption in this region (Fig. 1; cf. Riccoboni, *Gazzetta*, 1941, **71**, 696).

(ii) The Group V substituents NMe_2, PMe_2, $AsMe_2$, and $SbMe_2$ cause large bathochromic displacements which decrease as the group is ascended. The substituent NMe_2 also causes a large intensification of the *B*-band, but in Ph·PMe_2, Ph·$AsMe_2$, and Ph·$SbMe_2$ this band appears to be submerged. By contrast, the corresponding quaternary sub-

stituents NMe_3^+, etc., have only negligible effects; the light absorption of quaternary derivatives (*e.g.*, methiodides) of this group is completely different from that of the parent compounds and resembles that of benzene in the 2500 Å region (Fig. 3). (At shorter wave-lengths, the curves are not comparable because of the superimposed intense absorption of the iodide ion.)

(iii) The Group VI substituents OEt, SEt, SeEt, and TeEt produce similar displacements to those of Group V, except that the effect of OEt is relatively small.

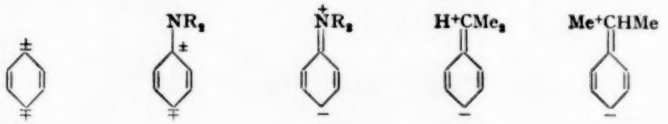
(iv) The Group VII substituents F, Cl, Br, and I cause relatively small effects; as the group is ascended, the *E*-band undergoes increasing bathochromic displacements with but little change in intensity, while the *B*-band undergoes only slight wave-length displacements, but a large increase in intensity in the case of PhF and PhI. The predicted, large auxochromic effect of a PR_2 substituent is confirmed,* but the earlier generalisation (Part III, *loc. cit.*), *viz.*, that the auxochromic effects increase as a Periodic Group is ascended, is now seen to be valid only for the first two rows of the Periodic System and in Group VII.

TABLE 2. *Ultra-violet absorption of* $Ph{\cdot}X{\cdot}R_n$.*

Group IV		Group V		Group VI		Group VII	
$\lambda_{max.}$	ε	$\lambda_{max.}$	ε	$\lambda_{max.}$	ε	$\lambda_{max.}$	ε
X = CMe_3		X = NMe_2		X = OEt		X = F	
2075	7800	2050	12000	2195	9500	2040	6200
		2510	14000				
2570	170	2980	2250	2720	1900	2540	900
X = $SiMe_3$		X = PMe_2		X = SEt		X = Cl	
2110	9300	2510	3500	2050	12500	2100	7500
				2550	8600		
2600	225	—		2780	1100	2570	170
X = $SnEt_3$		X = $AsMe_2$		X = SeEt		X = Br	
2040	18000	2390	6800	2500	4900	2100	8600
2510	850	—		2690	3200	2610	200
X = $PbMe_3$		X = $SbMe_2$		X = TeEt		X = I	
2060	27000	2500	3700	2250	14600	2260	13000
2560	1300	—		2700	4000	2560	800

* Data refer to ethanol solutions, except for $Ph{\cdot}PMe_2$ which was measured in *cyclo*hexane. Only the principal data are given in this table; for complete data see the Experimental section.

It will be convenient to consider separately the auxochromic effects on the *E*- and *B*-bands. In the terms of valence-bond resonance theory, the *E*-band in benzene may be regarded as arising from transitions to an excited state involving increased contributions from the *p*-dipolar structures † (I) (Craig, *Proc. Roy. Soc.*, 1950, *A*, **200**, 401) and is similar in character to the high-intensity *K*-bands of butadiene and related open-chain conjugated systems which involve dipolar structures such as $^{+}CH_2{-}CH{=}CH{-}CH_2{}^{-}$. On this basis, the almost identical *E*-bands near 2000 Å found in substituted benzenes are regarded as "partial" chromophore bands due to transitions involving only the ring and represented by structures such as (II*a*), whereas the new *E*-bands at longer wave-lengths are



(I) (II*a*) (II*b*) (III*a*) (III*b*)

associated with the new chromophore Ph·X. The bathochromic effects produced by substituents carrying unshared electron pairs are similar in the benzenoid and ethenoid systems (Table 1) and are ascribed to contributions from structures such as (II*b*).

* Since this paper was written, values similar to those for dimethylphenylphosphine have been reported for 1-phenyl*cyclo*tetramethylenephosphines (Fürst and Horvat, *Science*, 1951, **114**, 330).

† In the wave-mechanical treatment, contributions from *o*-dipolar and homopolar structures are also invoked, but the polarities of the various *o*-dipolar structures in the excited state cancel, whereas those of the *p*-dipolar structures do not.

Such contributions will lower the energies of both the ground and the excited states, and since they will be larger in the more highly polar excited state, the energy of the latter will be lowered more than that of the ground state, *i.e.*, the excitation energy will be decreased and the bands displaced to longer wave-lengths.* The fact that the unshared *p*-electrons of the substituents are involved is borne out by the fact that the bathochromic effects of the Group V substituents disappear almost entirely in the corresponding quaternary derivatives in which the *p*-electron pair is used in bond formation. No simple relation is apparent, however, between the magnitude of the bathochromic effects on the *E*-band and the ionisation potentials of the substituents, or similar parameters which might afford some measure of the availability of the *p*-electrons for electronic displacements of the type involved. Nor is there any exact correspondence between these spectral effects and the so-called "electromeric" effects in chemical reactivity, which are regarded as due to analogous, though less complete, electronic displacements; thus, whereas the bathochromic effects increase in the sequence F<Cl<Br<I, the electromeric effects increase in the reverse order (cf. Braude and Stern, *J.*, 1947, 1096; Baker and Hopkins, *J.*, 1949, 1089, and earlier references there cited).

The small, but definite auxochromic displacements produced by Group IV substituents, which do not possess unshared *p*-electron pairs, are less easily accounted for. Three explanations appear possible:

(i) The displacements may be due to interaction between the π-electrons of the ring and the σ-electrons of the substituent, *i.e.*, to contributions from hyperconjugated structures such as (III*a*) and (III*b*). The fact that locations of the *E*-bands are almost identical for toluene, ethylbenzene (Platt and Klevens, *loc. cit.*, 1947), and *tert.*-butylbenzene indicates that, if this mechanism is operative, interaction with the σ-electrons of carbon–hydrogen bonds and carbon–carbon bonds (*i.e.*, III*a* and III*b*) must be of almost equal importance. There is much evidence, however, that C=C–C–C hyperconjugation is much weaker than C=C–C–H hyperconjugation (cf. below) and it seems unlikely that this effect can be solely responsible for the displacements of *E*-bands by alkyl and similar groups.

(ii) A second possibility is that the displacements are due to a "proximity" or "inductive" effect, *i.e.*, to the electrostatic influence of the non-valency electron-cloud of the substituent. If this were the case, the displacements would be expected to *increase* in going from Ph·CMe_3 to Ph·$SiMe_3$, as observed (little significance can be attached to the data for Ph·$SnEt_3$ and Ph·$PbMe_3$ because of the superposition of absorption due to the metallic moiety itself in the *E*-band range). A similar increase would be expected in the sequence PhMe, PhEt, and PhBu; this, however, is not observed.

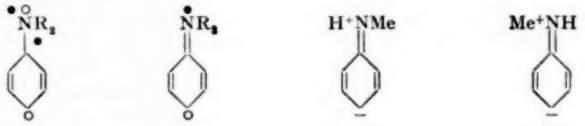
(iii) The displacements could arise simply from a "weighting" effect—an alteration in the relative populations of the vibrational sub-levels and of the relative heights of the submerged vibrational peaks, resulting in a shift in the centre of gravity of the band envelope. However, this explanation is again countered by the fact that the displacements actually *decrease* with increasing "weight" in the sequence PhMe, PhEt, and PhBu.

Nevertheless, it is probable that each of the three effects discussed makes some contribution in the case of Group IV as well as other substituents.

We now turn to the effects of substituents on the *B*-band, which may be ascribed to a forbidden transition involving increased contributions from homopolar excited (Dewar) structures (Sklar, *J. Chem. Physics*, 1937, **5**, 669; cf. Craig, *loc. cit.*). Auxochromic displacements of this band are less amenable to qualitative theoretical discussion, because the influence of substituents on the relative energy levels of Dewar structures is not easy to assess. However, it is clear that a substituent with an unshared electron pair will stabilise a Dewar structure such as (II*c*) in virtue of an electron pairing–unpairing process leading to (II*d*). The ease of the process represented by going from the classical structure to (II*c*) might

* There has been some controversy concerning the assignment of the high-intensity bands in substituted benzenes. Some authors (*e.g.*, Klevens and Platt, *loc. cit.*, 1949) have regarded the 2510 Å band in dimethylaniline as a strongly intensified *B*-band (2560 Å) of benzene. For reasons which will be apparent from the subsequent discussion, we believe the closeness of the two wave-length locations to be entirely coincidental and that it is the low-intensity band at 2980 Å of the amine which is related to the 2560 Å band of benzene.

be expected to bear some relation to the ease of going from the classical structure to (II*b*); in the valence-bond notation, the former involves the " migration " of *one*, and the latter that of *two* *p*-electrons into the ring. On the other hand, the relation will be modified by the fact that the former process does not, and the latter process does, involve the setting up of a formal charge. There is, in fact, some, though by no means exact, parallelism between the effects of substituents on the *E*- and the *B*-band.



(II*c*) (II*d*) (II*e*) (II*f*)

(• and o represent valency electrons of opposite spin.)

A semi-quantitative molecular-orbital treatment of the effect of substituents on the *B*-band has been given by Sklar (*J. Chem. Physics*, 1939, **7**, 984) and, more recently, by Matsen (*J. Amer. Chem. Soc.*, 1950, **72**, 5243; Robertson and Matsen, *ibid.*, p. 5248, 5252). Sklar dealt primarily with the effect of substituents on intensity, and concluded that a substituent will have a large effect if it has a pair of non-bonded *p*-electrons, a low ionisation potential, and not too large a Ph–X distance. On this basis, SH was predicted to be very effective; in fact, however, the *B*-bands of Ph·SH (Part III, *loc. cit.*; Robertson and Matsen, *loc. cit.*) as well as of Ph·SMe and Ph·SEt are rather less intense than those of Ph·NMe_2 or Ph·OMe. Matsen applied molecular-orbital theory to the calculation of wave-length displacements and derived an expression which predicts that the bathochromic shift of the *B*-band will be larger, the smaller the ionisation potential of the substituent X. As already noted by Robertson and Matsen (*loc. cit.*), this prediction is not fulfilled for the sequence Ph·NH_2, Ph·OH, and Ph·SH, and the present data for the sequence Ph·NMe_2, Ph·SEt, Ph·SeEt, and Ph·TeEt show that the wave-length shift of the *B*-band actually *decreases* with decreasing ionisation potential (NH_3 10·8, H_2S 10·5, H_2Se 9·8, H_2Te 9·14 e.v.; Price, *Chem. Reviews*, 1947, **41**, 257; Price, Teegan, and Walsh, *Proc. Roy. Soc.*, 1950, *A*, **201**, 600). The fact that charged substituents such as NR_3^+ cause displacements of the *B*-band comparable to those produced by a halogen substituent (Fig. 3), and that alkyl groups also have a marked, though smaller, effect, suggests that inductive influences play a considerable part.

Lastly, some interesting facts which emerge concerning the influence of R in Ph·XR_n may be briefly considered. It has long been known (cf. Wizinger, " Organische Farbstoffe," Berlin, 1933) that the bathochromic effect of alkylamino-groups in dyes increases in the order NH_2<NHMe<NMe_2. Similarly, the *E*-band of aniline is shifted by 210 Å towards longer wave-lengths in dimethylaniline compared with that of aniline, and an equal displacement is found in comparing thiophenol and methyl phenyl sulphide (Table 3).

TABLE 3. *Effects of alkyl substituents on band locations* ($\lambda_{max.}$, Å).

R	Ph·NR_2		Ph·OR		Ph·SR	
H	2300	2800 [1]	2100	2700 [3]	2350	2690 [1]
Me	2510	2980 [2]	2170	2690 [3]	2540	2790 [2]
Et	2580	3040 [2]	2195	2770 [2]	2550	2780 [2]

[1] Part III, *loc. cit.* [2] This paper. [3] Doub and Vandenbelt, *loc. cit.*

These effects, like those of alkyl groups attached directly to the phenyl ring (cf. p. 1073), could be either inductive or hyperconjugative in character, or both. If they were purely inductive, *i.e.*, due to the displacement of the *p*-electron pair of X towards the ring owing to electrostatic repulsion, they would be expected to increase in the sequence NH_2< NHMe<NMe_2<NEt_2 and SH<SMe<SEt, as observed. If, on the other hand, they were purely hyperconjugative, *i.e.*, due to contributions from structures such as (II*e*) and (II*f*), the displacements would be expected to be *smaller* for NMe_2 and SMe than for NH_2 and SH since X–H bonds are more polar than X–C bonds; thus, it is well known that

C–H hyperconjugation is stronger than C–C hyperconjugation (cf. Crawford, *Quart. Reviews*, 1949, **3**, 226; Bateman and Cunneen, *J.*, 1951, 2283). It therefore appears that the spectral effect of alkyl groups here is primarily inductive. In the alkylbenzenes, the auxochromic displacements of the *B*-band decrease in the sequence PhMe > PhEt > Ph·CMe$_3$ and this has been ascribed to hyperconjugation (Matsen, Robertson, and Chuoke, *Chem. Reviews*, 1947, **41**, 273). Hyperconjugation would not, however, be expected to exert a dominant influence in the case of *B*-bands which are due to almost non-polar transitions, and an alternative explanation has been given (Hammond, Price, Teegan, and Walsh, *Discuss. Faraday Soc.*, 1950, No. 9, p. 56).

Experimental

tert.-Butylbenzene was prepared in 70% yield from benzene and *tert.*-butanol by Berliner and Bondhus's modification (*J. Amer. Chem. Soc.*, 1946, **68**, 2355) of Huston, Fox, and Binder's method (*J. Org. Chem.*, 1938, **3**, 251). It had b. p. 167—168°/760 mm., $\lambda_{max.}$ in ethanol 2075, 2475, 2520, 2570, 2640, and 2670 Å, ε 7800, 110, 155, 170, 120, and 105, respectively.

Trimethylphenylsilane.—A solution of phenylmagnesium bromide (from Mg, 12 g.) in ether (200 ml.) was added to a stirred solution of silicon tetrachloride (85 g.) in ether (150 ml.) at 0°. After a further 30 minutes' stirring, the mixture was heated under reflux for 3 hours. It was then filtered, the residue was washed with ether, and the combined filtrate and washings were distilled, giving phenylsilicon trichloride (41 g.), b. p. 198—202°, as well as some higher-boiling products, probably diphenylsilicon dichloride. The trichloride (41 g.) in ether (50 ml.) was added dropwise to a solution of methylmagnesium iodide (from Mg, 15·3 g.) in ether (300 ml.) at 0°. The mixture was then heated for 3 hours under reflux and filtered hot. The filtrates were distilled, giving trimethylphenylsilane (21 g., 80%); b. p. 171—172°/760 mm. (cf. Bygdén, *Ber.*, 1912, **45**, 710). It had $\lambda_{max.}$ in ethanol 2110, 2470, 2530, 2600, 2650, and 2700 A, ε 9300, 75, 115, 225, 190, and 105, respectively.

Triethylphenyltin.—Tetraethyltin, b. p. 180°, prepared in 83% yield from stannic chloride (24 g.) and ethylmagnesium bromide (from Mg, 18 g.) in ether (300 ml.) (Pfeiffer and Schnurmann, *Ber.*, 1904, **37**, 320), was treated with the theoretical amount of bromine in carbon tetrachloride solution at 0°, giving triethyltin bromide, b. p. 107°/18 mm. (cf. Cahours, *Annalen*, 1860, **114**, 364). The bromide (18 g.) was added to a solution of phenylmagnesium bromide (from Mg, 1·52 g.) in ether (80 ml.) at 0°, and the whole heated under reflux for 1 hour; ice was added and the ethereal layer was separated and dried ($CaCl_2$). The ether was removed under reduced pressure and the product was distilled over a naked flame, giving triethylphenyltin (11 g., 62%), b. p. 134°/17 mm. (cf. Ladenburg, *Annalen*, 1871, **159**, 251). It had $\lambda_{max.}$ in ethanol 2040, 2060, 2080, 2510, 2560, and 2640 Å, ε 18 000, 17 000, 16 000, 850, 800, and 500, respectively.

Trimethylphenyl-lead.—Lead dichloride (56 g.) was added portionwise to an ethereal solution of methylmagnesium iodide at 0°. The mixture was heated under reflux for 1 hour and excess of ice was then added. The ethereal layer was separated, dried ($CaCl_2$), and treated with a solution of bromine (16 g.) in dry carbon tetrachloride (100 ml.) with external cooling in a carbon dioxide–methanol bath. After the addition, the mixture was allowed to attain room temperature and the solvents were removed under reduced pressure. The residue was extracted repeatedly with hot benzene and the extracts were concentrated under reduced pressure, giving trimethyl-lead bromide, m. p. 133° (Grüttner and Krause, *Ber.*, 1916, **49**, 1425, give m. p. 133°).

The bromide (17 g.) in hot benzene was added to an ice-cold ethereal solution of phenylmagnesium bromide (from Mg, 2 g.). The mixture was refluxed for 1 hour, then cooled to 0° and treated with ice-cold hydrochloric acid. The ethereal layer was dried ($CaCl_2$) and fractionated, giving trimethylphenyl-lead (16 g., 90%), b. p. 104°/15 mm. (cf. Grüttner and Grüttner, *Ber.*, 1918, **51**, 1294). It had $\lambda_{max.}$ in ethanol 2060 Å, ε 27 000; $\lambda_{infl.}$ 2560 and 2640 Å, ε 1300 and 800.

Dimethylaniline.—This had b. p. 79°/15 mm., $\lambda_{max.}$ in *cyclo*hexane 2510 and 2980 A, ε 14 000 and 2250; $\lambda_{max.}$ in ethanol 2510 and 2990 Å, ε 14 000 and 2100. The methiodide had $\lambda_{max.}$ in ethanol 2590 and 2640 Å, ε 430 and 250.

Diethylaniline, b. p. 182°/290 mm., showed $\lambda_{max.}$ in ethanol 2580, 2640, and 3040 Å, ε 16 000, 15 000, and 2250, respectively.

Dimethylphenylphosphine.—Phenyldichlorophosphine was prepared by continuous distillation of a mixture of equal volumes of benzene and phosphorus trichloride through a hard-glass tube heated to dull-red heat and packed with broken porous tile, in an atmosphere of carbon dioxide (cf. Arbuzov, *J. Russ. Phys. Chem. Soc.*, 1910, **42**, 395). The heated tube was con-

nected to a water-condenser leading back to the distillation flask. An ethereal solution of phenyldichlorophosphine (36 g.) was added dropwise to an ethereal solution of methylmagnesium iodide (from Mg, 14·4 g.) in an atmosphere of nitrogen. Next day, the solution was heated for 2 hours under reflux and then cooled to 0° and treated with excess of saturated aqueous ammonium chloride solution. The ethereal layer was separated, washed with water, dried (Na_2SO_4), and fractionated in a nitrogen atmosphere, giving dimethylphenylphosphine (12 g.), b. p. 79°/10 mm. (Meisenheimer *et al.*, *Annalen*, 1926, **449**, 227, give b. p. 83—84°/13·5 mm.). The phosphine, which is very readily oxidised in air, had $\lambda_{max.}$ 2510 Å, ε 3500 in dry *cyclo*hexane. Solutions in ethanol and dioxan gave variable values with lower intensities and were unsuitable for spectral measurements. The methiodide, crystallised from absolute ethanol, had m. p. 231—232° (Michaelis, *Annalen*, 1876, **181**, 363, gives m. p. 226—227°), $\lambda_{max.}$ in ethanol 2510, 2600, 2650, and 2720 Å, ε 450, 610, 920, and 810, respectively.

Dimethylphenylarsine.—This was prepared from dimethyliodoarsine and phenylmagnesium bromide (Burrows and Turner, *J.*, 1920, **117**, 1378). It was fractionated in a nitrogen atmosphere and had b. p. 85°/14 mm.; $\lambda_{max.}$ in *cyclo*hexane 2360, 2390, and 2420 Å, ε 6600, 6800, and 6600, respectively; $\lambda_{max.}$ in ethanol 2415 Å, ε 6800. The methiodide, crystallised from absolute ethanol, had m. p. 250° (Found: C, 38·1; H, 4·8. Calc. for $C_{11}H_{16}AsI$: C, 37·7; H, 4·6%) (Burrows and Turner, *loc. cit.*, give 250°), $\lambda_{max.}$ in ethanol 2500, 2560, 2620, and 2690 Å, ε 500, 600, 780, and 670, respectively.

Dimethylphenylstibine.—This was prepared by adding an ethereal solution of phenyldichlorostibine (Lecoq, *J. Pharm. Belg.*, 1937, **19**, 133) to an excess of methylmagnesium iodide in ether (cf. Grüttner and Wiernik, *Ber.*, 1915, **48**, 1759). It had b. p. 95—97°/10 mm., $\lambda_{max.}$ in ethanol 2500 Å, ε 3700. The stibine is rapidly oxidised in contact with air, and all manipulations were carried out in a nitrogen atmosphere. It formed a dibromide, m. p. 112° (from glacial acetic acid), $\lambda_{max.}$ in ethanol 2650 and 2700 Å, ε 610 and 430; $\lambda_{infl.}$ 2780 Å, ε 60, and a methiodide, m. p. 212° (decomp.) (from ethanol), $\lambda_{max.}$ in ethanol 2560, 2620, and 2670 Å, ε 480, 520, and 400, respectively. Phenetole had b. p. 172°/760 mm., n_D^{20} 1·5000, $\lambda_{max.}$ in ethanol 2195, 2720, and 2770 Å, ε 9500, 1900, and 1500, respectively. Methyl phenyl sulphide had b. p. 191°/760 mm., n_D^{20} 1·5810, $\lambda_{max.}$ in *cyclo*hexane 2540 Å, ε 9400; $\lambda_{infl.}$ 2790 Å, ε 1500; $\lambda_{max.}$ in ethanol 2050 and 2540 Å, ε 12 500 and 9400, $\lambda_{infl.}$ 2780 Å, ε 1400. Ethyl phenyl sulphide had b. p. 203°/755 mm., n_D^{20} 1·5740; $\lambda_{max.}$ in ethanol 2550 Å, ε 8600; $\lambda_{infl.}$ 2780 and 2880 Å, ε 1200 and 400. Ethyl phenyl selenide, prepared by the reaction of phenylmagnesium bromide with selenium, followed by treatment with ethyl iodide (Foster, *J. Amer. Chem. Soc.*, 1933, **55**, 822), had b. p. 216—218°/760 mm., $\lambda_{max.}$ in ethanol 2500, 2690, and 2790 Å, ε 4900, 3200, and 2600, respectively.

Ethyl Phenyl Telluride.—A suspension of tellurium (25·6 g.) in ether (100 ml.) was added to a stirred ethereal solution of phenylmagnesium bromide (from Mg, 4·8 g.) in a nitrogen atmosphere and the mixture was heated under reflux for 3 hours. Next day, ethyl iodide (31 g.) in ether (50 ml.) was added dropwise and the mixture was heated under reflux for one hour, then cooled; excess of ice-cold hydrochloric acid was added, and the ethereal layer was separated, washed with 30% aqueous sodium hydroxide and then with water, dried (Na_2SO_4), and distilled, giving *ethyl phenyl telluride* (20 g.) as a pale yellow liquid, b. p. 107—108°/22 mm. (Found: C, 41·1; H, 4·9. $C_8H_{10}Te$ requires C, 41·1; H, 4·3%); $\lambda_{max.}$ in *cyclo*hexane 2250, 2510, 2700, 3300 Å, ε 14 600, 3300, 4000, and 680, respectively; $\lambda_{max.}$ in ethanol 2240, 2510, and 2650 Å, ε 14 000, 4000, and 3500, respectively. Both solutions undergo rapid change on being kept, probably as a result of disproportionation into diphenyl telluride and diethyl telluride. The *ethiodide* separated from methanol in colourless crystals, m. p. 123° (Found: C, 31·2; H, 4·0. $C_{10}H_{15}ITe$ requires C, 30·8; H, 3·9%), $\lambda_{max.}$ in ethanol 2200 and 2600 Å, ε 29 500 and 2000; it rapidly darkens on exposure to air.

Fluorobenzene.—This had b. p. 83—84°, $\lambda_{max.}$ in ethanol 2040, 2480, 2540, 2600, 2660, ε 6200, 600, 900, 800, and 330, respectively; the light-absorption data in *cyclo*hexane were identical within experimental error. Chlorobenzene had b. p. 132°, $\lambda_{max.}$ in ethanol 2100, 2520, 2570, 2640, 2710 Å, ε 7500, 120, 170, 215, and 145, respectively. Bromobenzene had b. p. 157°, $\lambda_{max.}$ in ethanol 2100, 2510, 2610, 2640, and 2710 Å, ε 8600, 150, 180, 200, and 105, respectively. Iodobenzene had b. p. 188°, n_D^{24} 1·6162, $\lambda_{max.}$ in ethanol 2260 and 2560 Å, ε 13 000 and 800.

β-*Diethylaminostyrene.*—This amine was obtained as a colourless liquid in 80% yield by heating under reflux an ethereal solution of equimolar quantities of phenylacetaldehyde and anhydrous diethylamine in the presence of anhydrous sodium sulphate (cf. Mannich and Davidson, *Ber.*, 1936, **69**, 2106; Krabbe *et al.*, *ibid.*, 1941, **74**, 1892); b. p. 128°/7 mm. (Found: C, 82·1; H, 9·9. Calc. for $C_{12}H_{17}N$: C, 82·2; H, 9·8%) (Mannich and Davidson, *loc. cit.*, give b. p. 147—150°/16 mm.), $\lambda_{max.}$ in *n*-hexane 2280 and 3000 Å, ε 4900 and 12 800; $\lambda_{max.}$ in ethanol

2280 and 3050 Å, ε 4600 and 12 600. No reaction appeared to occur between phenylacetaldehyde and diethylphosphine under similar conditions.

trans-β-*Bromostyrene*.—This b. p. 104°/17 mm., m. p. 6° (cf. Wright, *J. Org. Chem.*, 1936, **1**, 459) and showed $\lambda_{max.}$ in ethanol 2530, 2560, and 2600 Å, ε 22 000, 23 000, and 22 000, respectively.

Light-absorption Measurements.—Measurements in the 2200—4000 Å region were made by the photographic method, a Hilger instrument being used (cf. Part I, *J.*, 1945, 490). Measurements in the 2000—2200 region were made by the photoelectric method by means of a Beckman instrument (cf. Part VII, *J.*, 1949, 1898). Contrary to some statements in the literature (cf. Moser, *Nature*, 1951, **167**, 656) absolute ethanol (*e.g.*, fractionated " Burnett's " alcohol) is sufficiently transparent for readings to about 2060 Å by the usual method, in which the instrument is calibrated with the solvent-cell in the beam. Below 2060 Å, a differential method must be used in which the instrument is calibrated without a cell in the beam. The extinctions of the solvent-cell and of the solution-cell are then taken in immediate succession and the reading for the first is subtracted from that for the second. The optical density (*E*) of a 1-cm. layer of highly purified ethanol at 2000 Å is *ca.* 1·5, corresponding to ε ~0·07, in good agreement with the figures given by Klevens and Platt (*J. Amer. Chem. Soc.*, 1947, **69**, 3059).

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190. *A New Synthesis of* 1-*Amino-4-methylthioxanthone and of Miracil D.*

By D. LL. HAMMICK and D. C. MUNRO.

Previous syntheses of these compounds have been carried out *via* 1-chloro-4-methylthioxanthone as an intermediate. The preparation of the latter compound is accompanied by formation of considerable amounts of the 4-chloro-1-methyl isomer.* The synthesis described here avoids the formation of such isomers, and leads more directly to the formation of 1-amino-4-methylthioxanthone (VI), which may be readily converted into Miracil D (VII) by reaction with 2-diethylaminoethyl chloride.

THE synthesis of Miracil D (1-2'-diethylaminoethylamino-4-methylthioxanthone hydrochloride) (VII) by the method of Mauss (*Ber.*, 1948, **81**, 19) requires the intermediate 1-chloro-4-methylthioxanthone. This substance has hitherto been prepared by the condensation of *o*-mercaptobenzoic acid with *p*-chlorotoluene, and is then accompanied by the isomeric 4-chloro-1-methylthioxanthone (40%) (Ullmann and von Glenck, *Ber.*, 1916, **49**, 2491).* The conversion of 1-chloro-4-methylthioxanthone into 1-amino-4-methylthioxanthone (VI) was brought about by these authors by interaction with toluene-*p*-sulphonamide, followed by hydrolysis.

During an investigation of the reactions of Miracil D and possible biological degradation products, a synthesis of such compounds was sought which avoided the formation of structural isomers and led more directly to the formation of 1-amino-4-methylthioxanthone. We have carried out such a synthesis, based initially on the preparation of 1-aminothioxanthone by F. Meyer (*Ber.*, 1909, **42**, 3064). Our sequence is shown in the scheme on p. 1078.

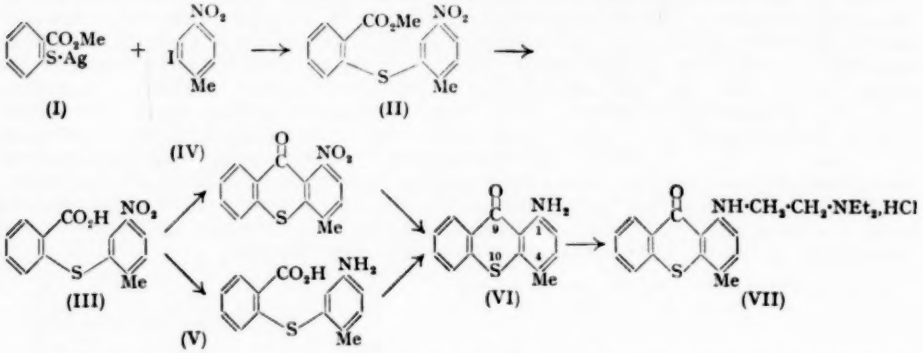
Methyl *o*-mercaptobenzoate, treated with ammoniacal silver nitrate in ethanol, readily gave an insoluble silver compound, presumably (I). This compound is stable at room temperature and is resistant to aerial oxidation in refluxing xylene. It is decomposed by concentrated hydrochloric acid. With 2-iodo-4-nitrotoluene in refluxing xylene, 2'-carbomethoxy-2-methyl-5-nitrodiphenyl sulphide (II) is formed, with elimination of silver iodide.

This reaction between 2-iodo-4-nitrotoluene and the silver compound appears to be

* *Added in Proof*.—Since this paper was submitted a synthesis of Miracil D *via* 1-chloro-4-methylthioxanthone and avoiding the formation of 4-chloro-1-methylthioxanthone has been described by Sharp (*J.*, 1951, 2961).

catalysed both by copper bronze and by cuprous iodide. Further investigations are being carried out on its applications.

The ester (II) may be hydrolysed by ethanolic sodium hydroxide below about 50°; above this temperature the formation of dark intractable material takes place.



Of three methods for the formation of the thioxanthone ring system, two were investigated for preparative purposes. The first involved ring closure of 2′-carboxy-2-methyl-5-nitrodiphenyl sulphide (III) by a Friedel–Crafts reaction using thionyl chloride and ferric chloride, subsequent reduction giving 1-amino-4-methylthioxanthone (VI). The second method, reduction of the nitro-acid to the corresponding amino-acid (V) followed by ring closure by the action of phosphoric acid was found to be more satisfactory in that the intermediate compound was more readily purified.

On being gently heated with acetic anhydride, 5-amino-2′-carboxy-2-methyldiphenyl sulphide (V) forms the normal acetyl derivative together with small amounts of 1-acetamido-4-methylthioxanthone. The former product is unchanged when heated alone or on dissolution in boiling acetic anhydride, but warm sulphuric acid causes the formation of 1-acetamido-4-methylthioxanthone.

1-Amino-4-methylthioxanthone (VI) reacts readily with 2-diethylaminoethyl chloride to form Miracil D (VII), and a convenient purification from the starting material is provided by the insolubility of the hydrochloride of 1-amino-4-methylthioxanthone in mixtures of ethanol and water, and in acetone.

Experimental

(All m. p.s are uncorrected.)

Methyl o-Mercaptobenzoate.—This was prepared from the acid by methanol and hydrogen chloride (Gatterman, *Ber.*, 1899, **32**, 1150), in 74% yield; it had b. p. 135—136°/15 mm.

Silver compound. The ester (20·5 g.) in ethanol (100 ml.) was added to a solution of silver nitrate (20 g.) in water (50 ml.), ammonia solution (20 ml.; *d* 0·880), and ethanol (200 ml.). The precipitate was filtered off, washed by stirring in ethanol (300 ml.), again filtered off, and dried in air at 100°. The *silver* derivative (yield, 96·5%) is a lemon-yellow powder, insoluble in water and in organic solvents, decomposed by hydrogen sulphide and by concentrated hydrochloric acid. It slowly softens with decomposition at 250° (Found: C, 34·95; H, 2·8; Ag, 39·7. $C_8H_7O_2SAg$ requires C, 34·9; H, 2·6; Ag, 39·2%).

2-*Iodo*-4-*nitrotoluene.*—2-Amino-4-nitrotoluene (30 g.) was diazotised and treated with potassium iodide (Willgerodt and Kok, *Ber.*, 1908, **41**, 2077). The crude product was taken up in ether, washed with sodium hydroxide solution and with water, and dried (Na_2SO_4). Removal of ether was followed by distillation at 15 mm. from an oil-bath at 210—230°. The distillate, b. p. 164—165°/15 mm., solidified, was washed with ether, filtered off, and dried. Further amounts were recovered from the ether after washing to remove traces of iodine, and also by exhaustive steam-distillation of the distillation residue. The yield was 40 g. (78%) and the m. p. 56° (Willgerodt and Kok give m. p. 58°). Distillation at reduced pressure enabled a tedious steam-distillation to be avoided; but attempted distillation of the crude material without the preliminary ether-treatment sometimes led to explosive decomposition.

Diphenyl Sulphide Formation.—The foregoing silver compound (40 g.), 2-iodo-4-nitrotoluene (38 g.), copper bronze (5 g.), and xylene (500 ml.) were heated under reflux for 6 hours. On cooling, the silver iodide was removed by filtration and washed with hot xylene. The xylene was removed by distillation followed by steam-distillation, and the solid residue recrystallised from benzene and ligroin (yield, 29·3 g., 67%; on 1-g. scale, 79%). After three recrystallisations from benzene and *cyclo*hexane, *2′-carbomethoxy-2-methyl-5-nitrodiphenyl sulphide* appeared as colourless prisms, m. p. 119°, soluble in benzene, less so in ligroin or *cyclo*hexane, sparingly soluble in ethanol (Found: C, 60·0; H, 4·6; N, 4·4; S, 10·55. $C_{15}H_{13}O_4NS$ requires C, 59·5; H, 4·3; N, 4·6; S, 10·55%).

Hydrolysis. This methyl ester (32·0 g.) was dissolved in ethanol (1 l.) at 60° and cold 2% sodium hydroxide solution (300 ml.) added. After 24 hours, the liquid was decanted from unchanged ester; water (2 l.) was added and then excess of concentrated hydrochloric acid. The precipitated acid was filtered off, washed with water, and dried in air at 100°. The whole process was repeated with unchanged ester. The total yield was 29·6 g. (97%). Recrystallised three times from ethanol, the *acid* formed colourless plates, m. p. 187°, soluble in ethanol, benzene, glacial acetic acid, or dilute aqueous alkali (Found: C, 58·1; H, 3·8; N, 4·5. $C_{14}H_{11}O_4NS$ requires C, 58·2; H, 3·4; N, 4·5%).

5-Amino-2′-carboxy-2-methyldiphenyl Sulphide.—The nitro-acid (20 g.) was dissolved in water (300 ml.), ethanol (140 ml.), and ammonia solution (100 ml.; *d* 0·880). The whole was added to a solution of ferrous sulphate hydrate (140 g.) in water (800 ml.) at 100° and stirred. After 5 minutes the suspension was filtered, and the residue washed with dilute ammonia solution. The combined filtrates were boiled to remove ethanol and ammonia, and an excess of glacial acetic acid added; the *amino-acid* (16 g., 89%) crystallised. This compound is soluble in acids and alkalis, readily soluble in ethanol, methanol, and benzene. Recrystallisation from *n*-propanol gave colourless prisms, m. p. 186·5° (Found: C, 64·4; H, 4·7; N, 5·7. $C_{14}H_{13}O_2NS$ requires C, 64·8; H, 5·05; N, 5·4%).

5-Acetamido-2′-carboxy-2-methyldiphenyl Sulphide.—The amino-acid (0·80 g.) was dissolved in acetic anhydride (3·0 ml.) with anhydrous sodium acetate (*ca.* 30 mg.) and heated gently on a water-bath for 10 minutes. Water (15 ml.) was added and heating continued; on cooling, an oil separated which crystallised when rubbed with ethyl acetate. After three recrystallisations from ethanol, the *acetyl* compound appeared as white crystals, m. p. 208°, soluble in alcohols and in dilute aqueous alkali (Found: N, 4·4. $C_{16}H_{15}O_3NS$ requires N, 4·65%).

This compound (55 mg.) was refluxed with acetic anhydride (2·5 ml.) for 3½ hours: no ring closure took place. The colourless precipitate obtained on heating with water was completely alkali-soluble.

The acetyl compound (50 mg.) dissolved in warm concentrated sulphuric acid (1 ml.) to form a carmine-red solution. After 1 minute, addition of water precipitated a yellow solid which, recrystallised from benzene, had m. p. 178° (with 1-acetamido-4-methylthioxanthone, mixed m. p. 179°).

4-Methyl-1-nitrothioxanthone.—2′-Carboxy-2-methyl-5-nitrodiphenyl sulphide (27 g.) in pure dry benzene (1·6 l.) was heated with purified thionyl chloride (30 ml.) under reflux. After 3½ hours, hydrogen chloride evolution had ceased; anhydrous ferric chloride (20 g.) was added and, after 10 minutes, heating was resumed for 5 hours. After cooling the benzene solution contained yellow crystals of *4-methyl-1-nitrothioxanthone* (9·5 g.), and its evaporation gave a further 1·9 g. The tarry material remaining was boiled with glacial acetic acid, giving a brown powder. This was either purified by recrystallisation, twice from *cyclo*hexanone and once from acetic acid, or was used directly for reduction. The total yield was 18·2 g. (72%) of pale yellow plates, m. p. 271°, sparingly soluble in benzene and glacial acetic acid, more soluble in *cyclo*hexanone (Found: C, 62·1; H, 3·2; N, 4·5; S, 11·6. $C_{14}H_9O_3NS$ requires C, 62·0; H, 3·3; N, 5·2; S, 11·8%).

1-Amino-4-methylthioxanthone.—(*a*) 4-Methyl-1-nitrothioxanthone (13 g.), suspended in ethanol (30 ml.), was treated with a solution of ferrous sulphate (hydrated; 100 g.) in water (120 ml.) and heated to boiling. A solution of ammonia (50 ml.; *d* 0·880) in water (100 ml.) was added, and the mixture heated in boiling water for 5 hours, then filtered, and the solid residue dried at 120°. Extraction with ethanol (250 ml.) (Soxhlet), concentration, and cooling, yielded red needles, m. p. 133° (from ethanol; charcoal) (9·2 g., 79%) (Ullmann and von Glenck, *loc. cit.*, give m. p. 134°).

(*b*) To syrupy phosphoric acid (50 ml.; *d* 1·75) in a Pyrex flask at 175° 5-amino-2′-carboxy-2-methyldiphenyl sulphide (5·0 g.) was added slowly during 10 minutes, and the solution heated for a further 15 minutes. On cooling, the solution was poured into water (500 ml.), excess of

ammonia solution added, and the precipitated amine filtered off. On recrystallisation from ethanol, with charcoal, 3·83 g. (72%) were obtained.

Gaseous hydrogen chloride was passed into a hot solution of the amine in ethanol, the *hydrochloride* crystallising as colourless plates, hydrolysed by, and insoluble in, water, sparingly soluble in ethanol. Recrystallised from ethanol, this had m. p. 218° (Found: N, 5·1; S, 12·0; Cl, 13·4. $C_{14}H_{11}ONS,HCl$ requires N, 5·0; S, 11·55; Cl, 12·8%).

1-*Acetamido*-4-*methylthioxanthone*.—The amine (0·5 g.) and acetic anhydride (2·0 g.) were heated at 100° for 10 minutes, water (5 ml.) was added, and the mixture heated. The solid was filtered off, dried, and recrystallised twice from benzene, then melting at 180—181° (Ullmann and von Glenck, *loc. cit.*, give m. p. 180—181°).

Diethylaminoethyl Chloride.—Diethylaminoethanol was converted into diethylaminoethyl chloride hydrochloride by Gough and King's method (*J.*, 1928, 2436). The base was released with saturated potassium carbonate solution, ether-extracted, and distilled, and had b. p. 45°/12 mm.

Miracil D.—1-Amino-4-methylthioxanthone (2·0 g.) and diethylaminoethyl chloride (1·5 g.) were heated together in an oil-bath at 150° for 1 hour (cf. Mauss, *loc. cit.*, p. 28). The solid was dissolved in hot ethanol (25 ml.), and concentrated hydrochloric acid (25 ml.) added, followed by water (50 ml.). After 24 hours, the crystals of 1-amino-4-methylthioxanthone hydrochloride were filtered off. The filtrate was treated with sodium hydroxide solution to pH about 6 and evaporated to dryness at 30 mm. The residue was treated with ethanol (100 ml.), filtered to remove sodium chloride, and evaporated to dryness. Heating with ethanol (20 ml.), filtering, and cooling yielded crystals of Miracil D (0·77 g.). Further amounts (0·51 g.) were recovered from the mother-liquor by evaporation, treatment with acetone, filtration, evaporation, and crystallisation from ethanol. Recrystallised twice from methanol and ether, the substance appeared as a bright yellow powder, m. p. 192° (Mauss, *loc. cit.*, gives m. p. 195—196°).

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191. *Strychnine and Brucine. Part LIII.* Compounds of Phenols and Certain Strychnine Derivatives.*

By J. T. Edward and Sir Robert Robinson.

Methylstrychnine combines with many phenols, expecially polyhydric phenols, to give crystalline complexes which are not methylstrychninium salts. Such salts can however also be prepared and the two classes are readily distinguished from one another by characteristic colour reactions.

Benzylstrychnine and *N*(*b*)-hydroxystrychnine afford similar complexes.

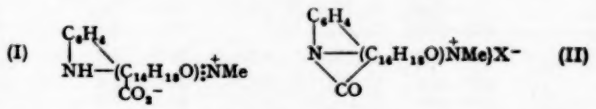
It is suggested that formation of these compounds provides the best known method for the isolation of polyhydric phenols from mixtures such as are obtained, for example, by the alkali-fusion of many natural products. The pure phenol may be recovered from the complex by treatment with hydrochloric acid and extraction with ether.

Compounds of methylstrychnine which are usually, but not invariably, derived from one molecule each of base and phenol, separate in beautifully crystalline forms when saturated aqueous solutions of the components are mixed. The crystals contain varying amounts of water of crystallisation (methylstrychnine–phloroglucinol is anhydrous) and have unsatisfactory melting points. Identification would be best effected by comparison of the crystals by well-established procedures. When heated under 0·2 mm. pressure, some of the complexes, for example, methylstrychnine–resorcinol, decompose. The phenol is

* Part LII, *J.*, 1952, 982.

volatilised and the residue has the melting point of methylstrychnine. The method of mixed melting points is useless in this series.

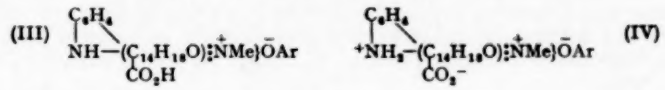
It is known that methylstrychnine (I) is a betaine converted by an acid HX into a methylstrychninium salt (II). Because (I) is an aniline derivative with a free *p*-position



it exhibits colour reactions of which the most convenient is the oxidative coupling by ferric chloride. This produces orange-red to carmine bisphenoquinimmonium salts. The acylated aniline derivative (II) shows no such behaviour but it does exhibit the Otto reaction which fails in the case of (I).

To our surprise methylstrychnine–resorcinol (and other similar complexes) exhibited the reactions of (I) and not those of (II). The behaviour on heating in a vacuum is also a proof that the substance is not the methylstrychninium resorcinol salt.

The most probable view of the constitution of these complexes is that they are indeed salts, but not lactams, and they may be formulated like (III) or (IV).



In solution the molecules cannot all be in the form (IV) because the nucleus of the substituted aniline salts is unreactive.

It is noteworthy that, whereas simple acids such as benzoic acid do not furnish well-crystallised complexes, phenolic acids, for example, salicylic and *p*-hydroxybenzoic acids, do so. The colour reactions show that the products are methylstrychnine complexes. For comparison with methylstrychnine–resorcinol, it was sought to obtain the true methylstrychninium resorcinol salt by interaction of methylstrychninium chloride and sodium resorcinoxide. A new compound was isolated and this gave the colour reactions of resorcinol and of the methylstrychninium salts but not those of methylstrychnine. Analysis showed that the substance was derived from two molecules of resorcinol and one of the methylstrychninium hydroxide.

Attempts to prepare this type of salt were made in several other cases but the products were uncrystallisable gums.

Benzylstrychnine gave complexes similar to those made from methylstrychnine but its use offers no advantages. *N*(*b*)-Hydroxystrychnine (the betaine from strychnine *N*-oxide, through strychnic acid *N*-oxide), however, furnished some good complexes. It suffers from the disadvantage of sparing solubility, even in hot water. Strychnine *N*-oxide formed a complex with quinol, but not with other polyhydric phenols.

A tendency to form complexes with phenols has been noted with various *Cinchona* alkaloids (cf. Rossignol and Riboulleau, *Compt. rend.*, 1939, **207**, 495).

Experimental

Methylstrychnine.—This compound, made according to the procedure of Clemo, Perkin, and Robinson (*J.*, 1927, 1624), had m. p. 303—304° (decomp.). Treatment of a hot concentrated aqueous solution with hydrochloric acid gave, on cooling, a felted mat of white needles of strychnininium methochloride, m. p. 295—296° (Found: C, 62·9; H, 6·7. Calc. for $C_{22}H_{25}O_2N_2Cl$: C, 62·7; H, 6·9%). Kotake and Mitsuwa (*Annalen*, 1933, **505**, 208) prepared this salt from the methiodide, and report m. p. 288—290°. It is much more readily soluble in water than methylstrychnine. *Methylstrychninium perchlorate* is sparingly soluble in water, from which it crystallizes in long needles, m. p. 309—310° (decomp.) (Found: C, 58·7; H, 5·7; N, 6·2; Cl, 8·0. $C_{22}H_{25}O_6N_2Cl$ requires C, 58·8; H, 5·6; N, 6·2; Cl, 7·9%).

Complexes of Phenols with Methylstrychnine.—The *complexes* recorded in the table were made

by mixing aqueous solutions of methylstrychnine and the phenol. In some cases [marked (*s*)] hot saturated solutions were mixed, because of the greater solubility of the complexes.

Phenol	M. p. of complex	Formula	Required, % C	H	N	Found, % C	H	N
Pyrogallol	214—215°	$C_{28}H_{32}O_6N_2,3H_2O$	61·5	7·0	—	61·6	6·9	—
Phloroglucinol	281—283	$C_{28}H_{32}O_6N_2$	68·3	6·6	—	68·8	6·8	—
Resorcinol	246—248	$C_{28}H_{32}O_5N_2,1{\cdot}5H_2O$	66·7	7·0	—	66·5 66·4	7·1 7·1	— —
Quinol	227—229	$C_{28}H_{32}O_5N_2,2H_2O$	65·7	7·1	—	66·1	6·9	—
p-Hydroxybenzaldehyde	213—216	$C_{29}H_{32}O_5N_2,2H_2O$	66·4	6·9	—	66·7	7·1	—
Catechol (*s*)	229	$C_{28}H_{32}O_5N_2,3{\cdot}5H_2O$	62·4	7·3	—	62·6	7·2	—
p-Hydroxybenzoic acid (*s*)	207—209	$C_{29}H_{32}O_6N_2,2H_2O$	64·5	6·7	—	64·8	6·9	—
p-Methoxyphenol (*s*)	200	$C_{36}H_{41}O_7N_2,3H_2O$	64·7	7·2	4·2	64·3	7·3	4·3
Salicylic acid (*s*)	192	$C_{29}H_{32}O_6N_2,0{\cdot}5H_2O$	67·9	6·5	—	68·3	6·3	—
Guaiacol (*s*)	308	$C_{29}H_{34}O_5N_2,5{\cdot}5H_2O$	59·1	7·7	4·8	59·3	7·4	5·1
Protocatechuic acid (*s*)	204—205	$C_{29}H_{32}O_7N_2,3H_2O$	60·7	6·7	4·9	60·5	7·0	4·9

The following phenols failed to give satisfactory derivatives; phenol, *o*- and *m*-aminophenol, *m*-cresol, *p*-chlorophenol, gentisic acid, gallic acid.

When the following complexes were made by mixing hot concentrated solutions, and then cooling, the m. p.s were: resorcinol–methylstrychnine, 251°; pyrogallol–methylstrychnine, 220—221°; phloroglucinol–methylstrychnine, 276—279°; quinol–methylstrychnine, 237—238°. The divergences from the previously observed m. p.s may be due to the different method of preparation and different content of water of crystallisation, as shown in the analysis for the *resorcinol–methylstrychnine* complex (Found: C, 65·9; H, 7·1. $C_{28}H_{32}O_5N_2,2H_2O$ requires C, 65·7; H, 7·1%).

Our experience suggests that the water of crystallisation in many of the complexes may be clathrate and it is certainly unusually subject to variation with the conditions of preparation. We have therefore calculated the water contents on the basis of determinations of carbon, which we regard as the most accurate, and wish expressly to avoid the suggestion of precise ratios of solvent of crystallisation.

It was noted that when the m. p. of resorcinol–, quinol–, or phloroglucinol–methylstrychnine (but not pyrogallol–methylstrychnine) was taken in a capillary continuously exhausted to a pressure of 0·2 mm. it was the same as that of methylstrychnine, indicating dissociation and sublimation of the phenol. The recovery was never satisfactory and this thermal decomposition cannot be recommended as a practical method of preparation.

Methylstrychninium Resorcinol Salt.—Resorcinol (0·3 g.) in water (4 c.c.) containing N-sodium hydroxide (3 c.c.) was added with shaking to a solution of strychnine methosulphate (1·0 g.) in water (5 c.c.). White plates crystallised from the cloudy solution; after recrystallisation from water these melted at 169—171° without decomposition to a clear liquid (Found, in air-dried material: C, 64·8; H, 7·2. $C_{34}H_{36}O_6N_2,3{\cdot}5H_2O$ requires C, 64·6; H, 6·9. Found, in material dried at 90°/10 mm.: C, 70·7; H, 6·7; N, 4·6. $C_{34}H_{36}O_6N_2,0{\cdot}5H_2O$ requires C, 70·7; H, 6·5; N, 4·9%). The Otto test using 60% sulphuric acid gave a brownish-purple colour; the ferric chloride reaction was a pale purple, like that for resorcinol itself.

Benzylstrychnine (cf. Achmatowicz, Clemo, Perkin, and Robinson, *J.*, 1932, 767).—Strychnine (34 g.) and benzyl chloride (12 c.c.) were triturated together, and after 1 day the mass was boiled with water (300 c.c.) and filtered from a small amount of unchanged strychnine. The slightly gummy needles of benzylstrychninium chloride were recrystallised twice from water (charcoal) and once from methanol. The large rhombs obtained melted at 283—284° (Found: C, 69·8, 70·0; H, 6·3, 6·3; N, 5·8. Calc. for $C_{28}H_{29}O_2N_2Cl,H_2O$: C, 70·2; H, 6·5; N, 5·8%). Treatment of a hot aqueous solution of the salt (10 g.) with aqueous potassium hydroxide (15 c.c. of 50%) gave a yellow oil which solidified on shaking and heating. The crude benzylstrychnine was purified by recrystallisation from water (charcoal) from which it separated as a mat of long needles. The m. p. was unsharp, above 220°; it was very sensitive to the rate of heating and was not raised by repeated recrystallisation of the substance from water (Found: C, 57·1; H, 8·2; N, 4·6. Calc. for $C_{28}H_{30}O_3N_2,8H_2O$: C, 57·3; H, 7·9; N, 4·8%).

Benzylstrychninium perchlorate, made by the action of perchloric acid on aqueous solutions of benzylstrychninium chloride or benzylstrychnine, had m. p. 301° (decomp.) and was very sparingly soluble in water. Consistent analytical results were not obtained for this compound, probably owing to explosive decomposition during combustion (Found: C, 63·6; H, 5·7. $C_{28}H_{29}O_6N_2Cl$ requires C, 64·1; H, 5·6%).

Complexes of Phenols with Benzylstrychnine.—These complexes are shown in the following table.

Phenol	M. p. of complex	Formula	Required, % C	H	N	Found, % C	H	N
Phloroglucinol	225—230°	$C_{34}H_{34}O_6N_2,8{\cdot}5H_2O$	56·6	7·4	3·9	56·9	7·7	4·0
Catechol	201	$C_{34}H_{34}O_6N_2,2{\cdot}5H_2O$	68·3	6·9	—	68·1	6·7	—
Gallic acid	182	$C_{35}H_{34}O_8N_2,2{\cdot}5H_2O$	63·9	6·3	—	63·9	6·5	—
Salicylic acid	213	$C_{35}H_{34}O_6N_2,2H_2O$	68·2	6·5	4·5	68·2	6·5	4·7
p-Chlorophenol	191	$C_{35}H_{35}O_4N_2Cl,8{\cdot}5H_2O$	57·1	7·1	3·8	57·2	7·4	4·2
Pyrogallol	195	$C_{34}H_{34}O_6N_2,2H_2O$	67·5	6·7	4·6	67·0	6·7	4·8

The mother-liquor from the salicylic acid–benzylstrychnine, m. p. 213°, slowly deposited another crystalline *complex*, having m. p. 190° and the composition 2 benzylstrychnine +1 salicylic acid +15 H_2O (Found: 58·9; H, 7·4; N, 4·4. $C_{63}H_{66}O_9N_4,15H_2O$ requires C, 58·5; H, 7·5; N, 4·3%).

The following phenols failed to give satisfactory derivatives and in many cases benzylstrychnine of varying m. p. was recovered: phenol, resorcinol, quinol, *o*- and *m*-aminophenol, *m*-cresol, gentisic acid, guaiacol, protocatechuic acid, *p*-methoxyphenol, *p*-hydroxybenzoic acid.

N(b)-*Hydroxystrychnine.*—The following procedure is simpler than that of Oesterlin (*Ber.*, 1943, **73**, 229). Strychnine *N*-oxide (Bailey and Robinson, *J.*, 1948, 703) (25 g.) in a solution of potassium hydroxide (13 g.) in water (250 c.c.) was heated on the steam-bath with occasional shaking for 3 hours. Next day, the cooled solution was acidified with glacial acetic acid (about 22 c.c.). The *N*(*b*)-hydroxystrychnic acid was collected and digested with hot ethanol (150 c.c.) which converted the mush into a white powder (13·6 g.), decomp. 215—216° (Found, in air-dried material: C, 64·5; H, 6·9. Calc. for $C_{21}H_{24}O_4N_2,1{\cdot}25H_2O$: C, 64·5; H, 6·8. Found, in material dried at 130°/15 mm. for 3 hours: C, 66·3; H, 6·6; N, 7·0. Calc. for $C_{21}H_{24}O_4N_2,0{\cdot}7H_2O$: C, 66·3; H, 6·6; N, 7·4%). Its solubility in hot alcohol and water was extremely small; from a hot solution of the latter it was recovered on cooling in ice in poor yield, m. p. 206—207° (Found: C, 64·9; H, 6·8%). It gave colour reactions (see below) indicative of a free $-N(a)H-$ group.

When the hot aqueous suspension was heated with hydrochloric acid, it dissolved, and then almost immediately strychnine *N*-oxide hydrochloride crystallised from the solution in prisms, darkening above 230° and decomposing at about 325° (Pictet and Mattisson, *Ber.*, 1905, **38**, 2785, report needles, darking above 250° and not melted at 310°). When a suspension of the salt was treated with sulphur dioxide, boiled, and made alkaline, strychnine (m. p. and mixed m. p.) was precipitated.

Strychnine *N*-oxide or *N*(*b*)-hydroxystrychnine, when heated with dilute perchloric acid, gave *N-hydroxystrychninium perchlorate*, very sparingly soluble in water, from which it crystallised in white needles, m. p. *ca.* 280° (decomp.) (Found: C, 54·0; H, 5·0; Cl, 7·3. $C_{21}H_{23}O_7N_2Cl,H_2O$ requires C, 53·8; H, 5·4; Cl, 7·6%).

Complexes of Phenols with N(b)-*Hydroxystrychnine.*—Because of the slight solubility of *N*(*b*)-hydroxystrychnine in water, the complexes were made by dissolving the appropriate phenol in a hot saturated solution of the betaine. On cooling, the *complex* crystallised out as a mat of soft, woolly needles. Details are give in the following Table.

Phenol	M. p. of complex	Formula	Required, % C	H	Found, % C	H
Resorcinol	211—212°	$C_{27}H_{30}O_6N_2,1{\cdot}5H_2O$	64·1	6·6	64·1	6·7
Phloroglucinol	220—221	$C_{27}H_{30}O_7N_2,H_2O$	63·3	6·3	63·6	6·6
Quinol	209—210	$C_{27}H_{30}O_6N_2,H_2O$	65·3	6·5	65·0	6·7
Catechol	165—166	$C_{27}H_{30}O_6N_2$	67·8	6·3	67·9	6·3
Phenol	199—200	$C_{27}H_{30}O_5N_2,1{\cdot}5H_2O$	66·2	6·8	65·8	6·7
Pyrogallol	about 170	$C_{27}H_{30}O_7N_2,2{\cdot}5H_2O$	60·2	6·5	60·0	6·6

Reaction of Strychnine N-*Oxide with Phenols.*—Addition of quinol to a hot aqueous solution of strychnine *N*-oxide gave, on cooling, tufts of rhombs, m. p. 191°, of a molecular *complex* (Found: C, 62·8; H, 6·9; N, 5·7. $C_{27}H_{28}O_5N_2,3H_2O$ requires C, 63·1; H, 6·7; N, 5·5%). In the Otto test with 60% sulphuric acid, this compound gave a transitory purple colour, instantly decolourized to a yellow, contrasting with the normal Otto test for strychnine *N*-oxide.

With the following phenols, strychnine *N*-oxide gave only gums: resorcinol, phloroglucinol, pyrogallol, catechol, protocatechuic acid, *p*-hydroxybenzoic acid, salicylic acid, *p*-methoxyphenol, gentisic acid, gallic acid.

Colour Reactions.—(a) *With ferric chloride.* Addition of one drop of ferric chloride solution to a suspension of the phenol complex (about 5 mg.) in water (1 c.c.) resulted in colours characteristic of the phenol or strychnine derivative, probably dependent on their relative reducing powers. The following complexes gave the same red colour as methylstrychnine: resorcinol–methylstrychnine; phloroglucinol–methylstrychnine, phloroglucinol–benzylstrychnine, resorcinol–*N*(*b*)-hydroxystrychnine, phloroglucinol–*N*(*b*)-hydroxystrychnine; *p*-chlorophenol–benzylstrychnine, *p*-hydroxybenzaldehyde–methylstrychnine, *p*-hydroxybenzoic acid–methylstrychnine, phenol–*N*-oxystrychnic acid. These colours, like those from methylstrychnine and other compounds having an opened lactam ring, change on storage for several hours through purple and port-wine colour to green; the red colour from strychnidine does not change.

The following complexes gave colours characteristic of the phenols: pyrogallol–methylstrychnine, –benzylstrychnine, and –*N*(*b*)-hydroxystrychnine (brown); quinol–methylstrychnine and –*N*(*b*)-hydroxystrychnine (pale gold); *p*-methoxyphenol–methylstrychnine (purple); salicylic acid–methylstrychnine (intense purple); guaiacol–methylstrychnine (yellow); protocatechuic acid–methylstrychnine (intense green); gallic acid–benzylstrychnine (green); catechol–methylstrychnine, –benzylstrychnine, and –*N*(*b*)-hydroxystrychnine (intense green). These colours did not change on storage

(b) *Otto test.* In the usual Otto test, one drop of potassium dichromate solution is added to a solution of about 10 mg. of substance in 1 c.c. of 60% sulphuric acid. Strychnidine and compounds with an opened lactam ring, such as methylstrychnine or *N*(*b*)-hydroxystrychnine give a permanent red; the same colour is given by most derivatives of phenols with methylstrychnine, benzylstrychnine, and *N*(*b*)-hydroxystrychnine. With the derivatives of certain phenols (salicylic acid, *p*-hydroxybenzoic acid, protocatechuic acid, *p*-chlorophenol, *p*-hydroxybenzaldehyde, phenol) this colour does not change; with derivatives of other phenols the colour changes, in a time varying from a few seconds to several hours, to one characteristic of the phenol. The final colours given by complexes of the following phenols are: catechol, black-green; quinol, faint green; resorcinol, madeira; pyrogallol, brown; *p*-methoxyphenol, pale yellow; guaiacol, deep purple; gallic acid, pale brown; phloroglucinol, pale brown.

In 96% sulphuric acid, strychnidine and methylstrychnine give no colour in the Otto test. No colour was given with complexes containing gallic acid, *p*-hydroxybenzoic acid, or protocatechuic acid; other complexes give colours ranging from reddish-brown to green, determined apparently by the phenol present.

Strychnine and most compounds containing a closed lactam ring give in either 60% or 96% sulphuric acid a transient series of colours, changing from purple to red and finally to yellow. With compounds containing a phenolic component (*e.g.*, the methylstrychninium resorcinol salt) the colours are slightly brownish, but the change is still quite recognisable. In no case did any of the molecular complexes give a result of this kind.

(c) *Persulphate test.* Potassium persulphate (about 50 mg.) added to a suspension of a compound containing the N(*a*)H group, such as methylstrychnine (10 mg.), in water (1 c.c.) gives on warming a deep red or black colour. Most complexes of methylstrychnine, benzylstrychnine, or *N*(*b*)-hydroxystrychnine with phenols behave in the same way. Strychnine gives no colour; neither does the methylstrychninium resorcinol salt. Strychnidine gives, very slowly, the red colour resulting with other oxidizing agents; this test furnishes a method for distinguishing between compounds with a reduced and a hydrolysed lactam ring, such as are typified by tetrahydrostrychnine and strychnidine.

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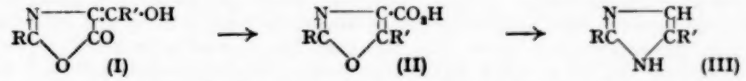
192. *Some Reactions of Oxazole-4-carboxylic Acids.*

By J. W. Cornforth and (in part) Mrs. E. Cookson.

The preparation of 2-substituted oxazole-4-carboxylic acids by rearrangement of the corresponding 4-hydroxyalkylideneoxazol-5-ones is described. Several of these acids were converted into glyoxalines. Novel reactions of 2-phenyloxazole-4-carboxylic acid include (*a*) nuclear methylation of the methyl ester by lead tetra-acetate, and (*b*) a Curtius degradation leading to ring-fission. The preparation of 2-benzamido-3-ketobutaldehyde (VI) extends the scope of a method previously reported.

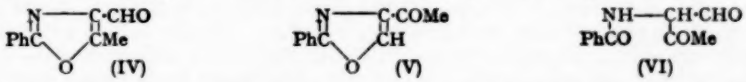
Oxazole-4-carboxylic acids substituted in the 2-position are conveniently prepared by rearrangement of 4-hydroxyalkylideneoxazol-5-ones, a general reaction illustrated in the change (I) ⟶ (II). The oxazolones (I) most readily available have an aryl or substituted vinyl group in the 2-position (Cornforth, " The Chemistry of Penicillin," Princeton Univ. Press, 1949, Ch. XXI).



The oxazolones (I) are preferably rearranged in the form of a sodium or potassium salt; ferric chloride is used to test for complete reaction, for (I) give a colour reaction and (II) do not. The temperature of reaction is high, and the heating should be as brief as possible; it is helpful to mix the oxazolone salt with sodium or potassium acetate to lower the fusion temperature, or alternatively to suspend the salt in liquid paraffin. Of the four oxazole-4-carboxylic acids (II; R = Ph or styryl, R′ = Me or H), one has already been made in this way (Cornforth and Huang, *J.*, 1948, 1960). The other three acids have now been prepared and converted into the corresponding glyoxalines (III) by heating them with aqueous ammonia (Cornforth and Cornforth, *J.*, 1947, 96; Cornforth and Huang, *loc. cit.*).

A reaction between lead tetra-acetate and methyl 2-phenyloxazole-4-carboxylate proceeded rapidly in acetic acid at 100° with evolution of gas, and the main product after hydrolysis was 5-methyl-2-phenyloxazole-4-carboxylic acid (II; R = Ph, R′ = Me). This nuclear methylation by lead tetra-acetate has been observed with naphthaquinones and various benzene derivatives (Fieser *et al.*, *J. Amer. Chem. Soc.*, 1942, **64**, 2043, 2052) but not to our knowledge with any heterocyclic system. It is the second substitution reaction so far observed in oxazoles, the other being a bromination (Brodrick *et al.*, *op. cit.*, p. 698).

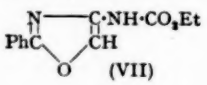
5-Methyl-2-phenyloxazole-4-carboxylic acid (II; R = Ph, R′ = Me) was converted by Rosenmund reduction of the acid chloride into the corresponding aldehyde (IV). It was necessary to distinguish this from the ketone (V) which might arise from it by re-



arrangement. The compound both reduced ammoniacal silver nitrate and gave a strongly positive iodoform reaction, but the aldehyde (IV) was indicated by the ready formation of a dimedone derivative. This aldehyde when shaken with cold dilute sodium hydroxide was slowly hydrolysed to 2-benzamido-3-ketobutaldehyde (VI); more drastic conditions destroyed the product. The reaction is analogous to a synthesis of acylaminomalondialdehydes already reported (Cornforth *et al.*, *J.*, 1949, 1549), but here the yield was poor.

As 4-amino-oxazole derivatives were unknown, the Curtius degradation of 2-phenyloxazole-4-carboxylic acid was studied. The acid chloride, azide, and *iso*cyanate were prepared by standard methods. The *iso*cyanate with alcohol yielded a normal urethane, 4-carbethoxyamino-2-phenyloxazole (VII). Attempts to prepare 4-amino-2-phenyl-

oxazole (VIII) from this compound or directly from the *iso*cyanate have been unsuccessful. Hydrolysis of the *iso*cyanate with cold fuming hydrochloric acid afforded a basic substance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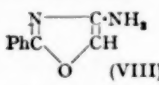
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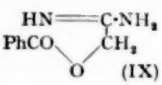
(IX)

which was conveniently isolated as the picrate. The product was shown to be *O*-benzoylglycollamidine (IX) by its synthesis from benzoyloxyacetonitrile *via* the imido-ether. This fission of an oxazole ring between atoms 2 and 3 is unique, though it is normal with Δ^2-oxazolines.

Experimental

4-*Ethoxymethylene*-2-*styryloxazol*-5-*one*.—Cinnamoylglycine (4 g.) was added gradually to a boiling (bath temp. 160°) mixture of ethyl orthoformate (5·5 c.c.), acetic anhydride (10 c.c.), and xylene (10 c.c.). The volatile products were distilled through a short fractionating column, the temperature at the top being controlled at about 110°. After addition was complete the mixture was heated for a few minutes (total time 25 min.) and then evaporated at 100°/20 mm. The dark residue was repeatedly extracted with boiling light petroleum (b. p. 80—100°). From the cooled extracts the light yellow crystalline oxazolone (2·2 g.), m. p. 102—103°, separated. The yield by this procedure is higher than that from the original preparation (*op. cit.*, p. 804).

The oxazolone (2·2 g.) in ether was shaken with sodium hydroxide (25 c.c.; 0·8N) until precipitation was complete. The product was collected, washed with ether, then a little water, and finally acetone, and dried (2·1 g.). This was the sodium salt of 4-hydroxymethylene-2-styryloxazol-5-one.

4-1′-*Hydroxyethylidene*-2-*styryloxazol*-5-*one*.—The sodium salt (19 g.) of cinnamoylglycine (prepared by precipitation of a neutral aqueous solution with acetone, and dried at 140° for 10 hours) was stirred vigorously for 5 hours with acetic anhydride (25 c.c.) and dry pyridine (26 c.c.), moisture being excluded. Ethanol (17 c.c.) was added dropwise, the temperature being kept at 30—35° by cooling. Stirring was continued for another hour; water (200 c.c.) was then added and the mixture was acidified to Congo-red (external cooling). The crude yellow solid was dissolved in one equivalent of sodium hydroxide (2N) and the filtered solution after being boiled (charcoal) was treated with hydrochloric acid. Recrystallization of the precipitated solid from ethyl acetate gave yellowish plates (10 g.), m. p. 218—219° undepressed by a sample prepared by the method (18% yield) previously reported (*op. cit.*, p. 830).

2-*Phenyloxazole*-4-*carboxylic Acid*.—A saturated ethereal solution of 4-ethoxymethylene-2-phenyloxazol-5-one (20 g.) was shaken with sodium hydroxide (50 c.c., 2N) for 2 hours or until precipitation appeared to be complete. The *sodium* salt of 4-hydroxymethylene-2-phenyloxazol-5-one (12 g.) was obtained in colourless plates by recrystallizing the ether-washed, dried precipitate from ethanol; it had m. p. 254—255° (decomp.) (Found : N, 6·1. $C_{10}H_6O_3NNa,H_2O$ requires N, 6·1%).

A powdered mixture of the sodium salt (2 g.) and sodium acetate (1 g.) in a thin-walled test-tube was introduced into a metal-bath maintained at 290—300°. The contents were stirred with a glass rod until the melt gave with aqueous ferric chloride no green colour extractable with ethyl acetate (about 5 minutes). The cooled melt was boiled in water (10 c.c.) with charcoal for 2 minutes and then filtered through charcoal. 2-Phenyloxazole-4-carboxylic acid (1·4 g.) was obtained by addition of acid to the filtrate and recrystallization of the precipitate from benzene; fine colourless needles, m. p. 210° undepressed by authentic material, were obtained.

2-*Styryloxazole*-4-*carboxylic Acid*.—The sodium salt of 4-hydroxymethylene-2-styryloxazol-5-one (2·15 g.) was suspended in liquid paraffin (5 c.c.) and stirred at 280° until the ferric chloride test was negative (about 10 minutes). The cooled mixture was treated with dilute hydrochloric acid and with ether–chloroform, and filtered to break an emulsion. The organic layer was extracted with very dilute aqueous ammonia. The acid precipitated from the ammonia extracts was dried and recrystallised from ethyl acetate. The *acid* separated in colourless leaflets (1·10 g., and 0·155 g. second crop), m. p. 199·5—200·5° (Found : C, 67·1; H, 3·9. $C_{12}H_9O_3N$ requires C, 67·0; H, 4·2%).

5-*Methyl*-2-*styryloxazole*-4-*carboxylic Acid*.—4-1′-Hydroxyethylidene-2-styryloxazol-5-one (1·075 g.) was stirred for a few minutes with alcoholic potassium hydroxide (10 c.c.; 0·5N). The solid remaining after evaporation of the alcohol was mixed with potassium acetate (0·5 g.)

and transferred to a test-tube which was then placed in a metal-bath at 290°. After being stirred for 5 minutes the melt gave a negative test with ferric chloride. A charcoal-treated, filtered aqueous solution of the melt was treated at the boiling-point with dilute hydrochloric acid. The crystalline precipitate was recrystallized from benzene; the *acid* (0·45 g.) separated in needles, m. p. 183—185° (Found: C, 67·8; H, 4·8. $C_{13}H_{11}O_3N$ requires C, 68·1; H, 4·8%).

Glyoxalines from Oxazole-4-carboxylic Acids.—The acid was dissolved in aqueous ammonia (about 10 c.c./g.; *d* 0·88), and the solution heated in a sealed tube. The basic product was isolated in the normal manner, the following glyoxalines being obtained.

2-Phenylglyoxaline, from 2-phenyloxazole-4-carboxylic acid in ammonia at 200° for 8 hours, formed colourless plates (45% yield), m. p. 149—150°, from aqueous ethanol (Found: C, 74·8; H, 5·3. Calc. for $C_9H_8N_2$: C, 75·0; H, 5·6%). *2-Styrylglyoxaline*, from 2-styryloxazole-4-carboxylic acid in ammonia at 190° for 24 hours, formed colourless needles (yield 20%), m. p. 178—179°, after sublimation at 180°/0·05 mm. and recrystallization from benzene (Found: C, 77·2; H, 6·0. $C_{11}H_{10}N_2$ requires C, 77·6; H, 5·9%). The ethereal solution had a blue fluorescence.

4-Methyl-2-styrylglyoxaline was obtained from 5-methyl-2-styryloxazole-4-carboxylic acid in ammonia at 240° for 9 hours. It formed colourless needles (25% yield), m. p. 232—233°, from ethyl acetate (Found: C, 78·0; H, 6·8; N, 15·0. Calc. for $C_{12}H_{12}N_2$: C, 78·2; H, 6·5; N, 15·2%); John (*Ber.*, 1935, **68**, 2289) records m. p. 235°. The preparation of 4-methyl-2-phenylglyoxaline from 5-methyl-2-phenyloxazole-4-carboxylic acid has already been described (Cornforth and Huang, *loc. cit.*).

Nuclear Methylation of Methyl 2-Phenyloxazole-4-carboxylate.—2-Phenyloxazole-4-carboxylic acid (3·25 g.) in dry methanol (20 c.c.) was treated with acetyl chloride (2 c.c.). After one hour's refluxing, water was added and the mixture made alkaline. The crystalline *methyl* ester (3·25 g.; m. p. ~80°) was collected; a sample recrystallized from light petroleum (40—60°) formed colourless silky needles, m. p. 85·5—87° (Found: N, 6·8. $C_{11}H_9O_3N$ requires N, 6·9%). Lead tetra-acetate (6·9 g.) was added to the ester (3·15 g.) in acetic acid (25 c.c.; purified). On heating to 105° there was a brisk evolution of gas and after 15 minutes the tetra-acetate had all been consumed. A further 3·45 g. of tetra-acetate was also reduced quite rapidly. The mixture was diluted with water and extracted twice with ether; the ether was washed with aqueous sodium carbonate and evaporated. The partly crystalline residue was heated for 15 minutes (steam-bath) with aqueous sodium hydroxide (15 c.c.; 2N) and a little alcohol, and the solution was diluted with water and acidified. One crystallization from alcohol and two from benzene gave 5-methyl-2-phenyloxazole-4-carboxylic acid, m. p. 179—180·5°. A mixture with an authentic specimen, m. p. 181—182°, had m. p. 180·5—182° (Found: N, 6·6. Calc. for $C_{11}H_9O_3N$: N, 6·9%). The crude acid was apparently contaminated with some unmethylated material.

5-Methyl-2-phenyloxazole-4-aldehyde.—5-Methyl-2-phenyloxazole-4-carboxylic acid (2 g.) was refluxed with thionyl chloride (1·2 c.c.) until the solid had dissolved. Recrystallization of the product from thiophen-free benzene gave prisms, m. p. 133—135°, of the acid chloride. This product (1 g.) with xylene (6 c.c.) and palladium–barium sulphate (0·5 g.) were refluxed in a current of hydrogen. Within 2 hours 92% of the theoretical quantity of hydrogen chloride had been evolved. Evaporation of the filtered xylene solution left a crystalline residue which was recrystallized from a little alcohol and washed with chilled (−25°) alcohol. The *aldehyde* formed colourless needles, m. p. 90·5—91·5° (Found: C, 70·2; H, 5·3; N, 7·8. $C_{11}H_9O_2N$ requires C, 70·6; H, 4·9; N, 7·5%). A *dimedone* derivative was prepared in the usual way; it crystallized from alcohol in colourless aggregated prisms, m. p. 263—264°, and appeared to be in the unusual anhydro-form (Found: C, 74·7; H, 7·0. $C_{27}H_{29}O_4N$ requires C, 75·1; H, 6·8%).

2-Benzamido-3-ketobutaldehyde.—The above aldehyde (132 mg.) was shaken overnight with sodium hydroxide (3 c.c.; 0·5N). The solution was filtered and the alkali-insoluble residue again shaken overnight with fresh alkali. From the united alkaline filtrates by acidification and ether extraction the *keto-aldehyde* was obtained; when recrystallized from light petroleum (b. p. 60—80°) and then from a little ether, there were obtained prismatic needles (10 mg.), m. p. 86° (Found: C, 64·8; H, 5·5. $C_{11}H_{11}O_3N$ requires C, 64·4; H, 5·4%). The aldehyde dissolved easily in alkali hydroxides and the neutral solution gave a blood-red colour with ferric chloride. The main reaction product was yellowish, alkali-insoluble, and apparently polymeric.

Curtius Degradation of 2-Phenyloxazole-4-carboxylic Acid.—Sodium azide (0·7 g.) in water (3 c.c.) was cooled to 0° and added gradually with good stirring to a similarly cooled solution

of 2-phenyloxazole-4-carboxychloride (2·07 g.) in acetone (25 c.c.); 20 minutes after the addition was completed, water (75 c.c.) was added, and the crude azide (2 g.), m. p. 120—121° (decomp.), collected and dried. It was refluxed in dry xylene (10 c.c.) until effervescence ceased (about 5 mins.). The cooled solution was shaken with aqueous hydrochloric acid (7 c.c.; saturated at 0°) at about 25°, again until effervescence ceased (10 minutes). The separated lower layer was diluted with water (40 c.c.), cooled, filtered, overlaid with ether, chilled in ice–salt and treated (swirling) with a concentrated aqueous solution of potassium carbonate (25 g.). A precipitate of carbamate separated in the ether; it was collected, and the ethereal layer separated and evaporated. The carbamate was treated with aqueous picric acid; the residue from the ether evaporation was dissolved in a little alcoholic picric acid and aqueous picric acid added as long as crystalline material separated. The two picrates were united (803 mg.) and recrystallized from methanol, giving 643 mg. of material, m. p. 207—209°. Another crystallization from methanol and one from *iso*propanol gave yellow needles, m. p. 215—216° (decomp.) of the *picrate* (Found: C, 44·2, 44·4; H, 3·8, 3·7; N, 16·6. $C_{10}H_{10}O_2N_2,C_6H_3O_7N_3$ requires C, 44·2; H, 3·2; N, 16·7%). In another experiment the solid carbamate was decomposed with sodium hydroxide in the presence of ether. Recrystallization from anhydrous ether gave the *base* in boat-shaped prisms, m. p. 88° (Found: C, 61·0; H, 6·1; N, 15·3. $C_{10}H_{10}O_2N_2$ requires C, 60·7; H, 5·7; N, 14·7%). The base decomposed with evolution of ammonia when warmed with dilute sodium hydroxide solution.

Benzoyloxyacetonitrile (2 g.) in dry ethanol (0·58 g.) was cooled slightly during the passage of dry hydrogen chloride. The mixture solidified when two-thirds of the theoretical amount had been absorbed. Next day the solid was collected (dry ether) and dried (NaOH). This imido-ether hydrochloride (1·65 g.) was suspended in a little ethanol and treated with one equivalent of ethanolic ammonia. Next day water was added, followed by aqueous picric acid until precipitation was complete. Recrystallization from methanol gave O-*benzoylglycollamidine picrate* as yellow needles (1·8 g.), m. p. 215—216° unchanged by recrystallization from *iso*propanol (Found: C, 44·0; H, 4·2; N, 16·6%). The m. p. was not depressed on admixture with the picrate from the Curtius degradation (above). A specimen was converted into the base; O-*benzoylglycollamidine* had m. p. 88°, undepressed by the Curtius degradation product. The base appeared to be dimorphic, for needles m. p. above 100° were first deposited, then giving place to the characteristic boat-shaped prisms.

4-*Carbethoxyamino*-2-*phenyloxazole*.—When the crude azide (1 g.) was decomposed in xylene as above and the product was boiled with ethanol for 3 hours, the *urethane* separated from the concentrated solution and was recrystallized from *cyclo*hexane; it formed colourless prisms (0·58 g.), m. p. 105° (Found: C, 62·1; H, 5·3. $C_{12}H_{12}O_3N_2$ requires C, 62·1; H, 5·2%).

One of us (J. W. C.) thanks Mrs. P. Perkins for assistance with the preparations.

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193. *The Chemistry of Ximenynic Acid.*

By S. P. Ligthelm, H. M. Schwartz, and M. M. von Holdt.

The isolation of ximenynic acid from the kernel oils of three *Ximenia* species is described. Degradative experiments show the acid to be heptadec-10-en-8-yne-1-carboxylic acid, but attempts to produce isomerisation about the double bond and to reduce the acid to the corresponding conjugated dienoic acid were unsuccessful. When heated with alkali at 180—190°, ximenynic acid isomerises to a conjugated trienoic acid.

The behaviour of ximenynic acid and its methyl ester towards the Wijs, Woburn, and Rosenmund–Kuhnhenn reagents has been studied. Ximenynic acid and its derivatives autoxidise readily, but the glycerol, pentaerythritol, and inositol esters are not suitable for use as drying oils.

In a preliminary communication (Ligthelm and Schwartz, *J. Amer. Chem. Soc.*, 1950, **72**, 1868), the isolation of an acid, $C_{18}H_{30}O_2$, from the kernel oils of three South African *Ximenia* species was described. The acid was named ximenynic acid, and it was shown to be a C_{18}

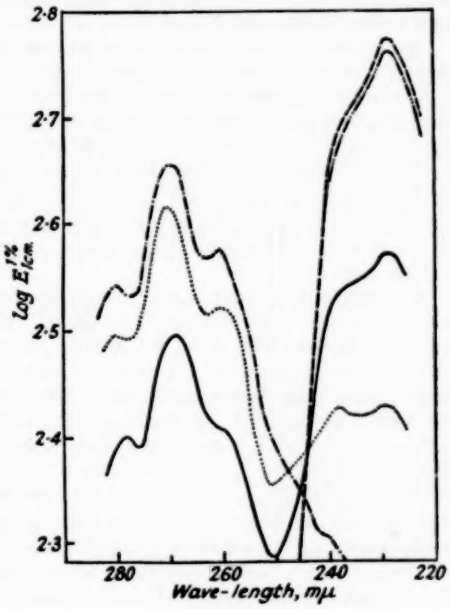
straight-chain acid containing one double and one triple bond. From the products of its oxidation with potassium permanganate and from the absorption spectrum of ximenynyl alcohol (Ligthelm, von Rudloff, and Sutton, *J.*, 1950, 3187), it was clear that the acid is either (I) or (II). We now report a further examination of the acid, that of the oils being

(I) $CH_3 \cdot [CH_2]_5 \cdot CH{:}CH \cdot C{\equiv}C \cdot [CH_2]_7 \cdot CO_2H$ $\qquad$ $CH_3 \cdot [CH_2]_5 \cdot C{\equiv}C \cdot CH{:}CH \cdot [CH_2]_7 \cdot CO_2H$ (II)

recorded elsewhere (*J. Sci. Food Agric.*, in the press).

Ximenynic acid is best isolated from the mixed acids of *Ximenia* oils by a combination of low-temperature crystallisation and high-vacuum distillation, an improvement in the former process being described on p. 1090. Ximenynic acid of 90—95% purity can also be obtained in good yield by chromatography of the acids or methyl esters on silica gel (Riemenschneider, Herb, and Nichols, *J. Amer. Oil Chem. Soc.*, 1949, **26**, 371) or alumina (Swift, Rose, and Jamieson, *Oil and Soap*, 1943, **20**, 249), especially when the starting mixtures contain more than 50% of the acid or ester. Preliminary concentration of ximenynic acid may be effected by formation of the urea complex from the total acids or the methyl esters (Schlenk and Holman, *J. Amer. Chem. Soc.*, 1950, **72**, 5001); *e.g.*, a single fractionation by this method of the total methyl esters of *Ximenia caffra* oil raised the methyl ximenynate content from 27 to 50% in the raffinate, but further concentration was not attained by refractionation. The urea complexes of the acid, methyl ester, and alcohol have been prepared, and their properties recorded. The " yield value " (Schlenk and Holman, *loc. cit.*) of the ester is lower than that of the acid and hence the former was used in the above purification experiments.

The ultra-violet absorption spectrum of the purest specimen of ximenynic acid obtained is shown in the figure, together with that of ximenynyl alcohol. Both compounds exhibit the main peak (at 229 mμ) characteristic of conjugated enynes; the inflections of low intensities near 268 mμ are attributed to the presence of a trace (*ca.* 0·1%) of conjugated triene acid which accompanies the ximenynic acid during purification.



— · · — *Ximenynic acid.*
— — — *Ximenynyl alcohol.*

Ximenynic acid after isomerisation by alkali for : 25 min. ——; *60 min.* – – – –; *120 min.* — · — · —.

Ozonolysis of ximenynic acid followed by decomposition of the ozonide with zinc and acetic acid (Noller and Adams, *J. Amer. Chem. Soc.*, 1926, **48**, 1074) gave *n*-heptanaldehyde and azelaic acid in quantity, and a trace of what was possibly azelaic semialdehyde derived from the conjugated triene impurity. It follows that ximenynic acid is heptadec-10-en-8-yne-1-carboxylic acid (I). Attempts to confirm this structure by synthesis and to determine whether the ethylenic bond has the *cis*- or the *trans*-configuration are in progress. Since most natural fatty acids have the *cis*-configuration, attempts were made to effect a *cis–trans*-change in ximenynic acid by heating it with selenium (Swern, Knight, Shreve, and Heether, *J. Amer. Oil. Chem. Soc.*, 1950, **27**, 17), but only unchanged acid was obtained.

When the acid or its methyl ester is heated with potassium hydroxide in ethylene glycol at 180—190° the maximum at 229 mμ is replaced by maxima at 260, 268, and 280 mμ characteristic of conjugated trienoic acids. The intensity of the central (268 mμ)

absorption band reaches a maximum after 120 minutes at 180° or 60 minutes at 190° (see figure); longer heating causes diminution in the intensity, presumably owing to subsequent polymerisation of the triene system. No change in the absorption spectrum of ximenynic acid, except a slight lowering of intensity, occurs when it is heated in ethylene glycol in the absence of alkali. Lithium aluminium hydride reduction of the crude isomerised acids gives a product with the same three absorption bands but of slightly greater intensity, indicating that no conjugation exists between the carbonyl group and the chromophoric system. A small yield of a crystalline acid, m. p. 60—61°, $E^{1\%}_{1\,cm.}$ 1705 at $\lambda_{max.}$ 268 mμ, was obtained by recrystallisation of the crude alkali-isomerised product. The products of permanganate oxidation of this acid appeared to contain mixtures of mono- and di-carboxylic acids, suggesting that isomeric heptadecatriene-1-carboxylic acids were present in the material of m. p. 60—61°; attempts to identify the oxidation products are being made. The isomerisation with alkali of the enyne system to a conjugated triene is of interest since Maruyama and Suziki (*Proc. Imp. Acad. Tokyo*, 1931, **7**, 265) reported the the conversion of heptadeca-7 : 9-diene-1-carboxylic acid into stearolic acid under similar conditions.

Attempts to convert the enyne system of ximenynic acid into the corresponding conjugated diene by partial hydrogenation by using a quinoline-poisoned palladium catalyst (Isler, Huber, Ronco, and Kofler, *Helv. Chim. Acta*, 1947, **30**, 1911) were unsuccessful; the products had less intense absorption in the 229—234 mμ region, whereas heptadeca-8 : 10-diene-1-carboxylic acid has $E^{1\%}_{1\,cm.}$ 1100 at $\lambda_{max.}$ 232 mμ. Attempted reduction with sodium and alcohol gave a product with lower intensity at 229—234 mμ. However, catalytic hydrogenation of ximenynyl alcohol by means of the quinoline-poisoned catalyst gave an increased ultra-violet absorption ($E^{1\%}_{1\,cm.}$ 670 at 229 mμ), indicating the formation of some of the desired conjugated diene system, but the experiments were too unpromising for further study.

It is well known that many acetylenic compounds add one mol. of halogen readily, but the second mol. with difficulty (Johnson, " The Chemistry of the Acetylenic Compounds," Arnold, London, Vol. 2, p. 57, 1950). In conformity, ximenynic acid gave low iodine values (absorption of *ca.* 1·5 moles of halogen per mole) with the Woburn (von Mikusch and Frazier, *Ind. Eng. Chem. Anal.*, 1941, **13**, 782) and the Wijs method (" Official and Tentative Methods of the American Oil Chemists' Society," Chicago, 1946), but values corresponding to *ca.* 2 moles per mole with the modified Rosenmund–Kuhnhenn method (Benham and Klee, *J. Amer. Oil Chem. Soc.*, 1950, **27**, 127, 130). If the reaction time in the Woburn method was increased to 96 hours, an addition of 2 moles per mole was obtained, and addition of bromine vapour to the acid or its methyl ester gave a similar result (private communication from Dr. F. Hawke).

Methyl ximenynate autoxidises rapidly in air and the parent acid does so more slowly. The glycerol, pentaerythritol, and inositol esters were prepared and tested for drying properties on glass plates in the presence of inorganic driers; the speed of setting increased in that order, but all the films remained tacky for at least 48 hours.

Experimental

($E^{1\%}_{1\,cm.}$ values were measured in *cyclo*hexane, except where otherwise stated.)

Isolation of Ximenynic Acid.—(a) *Preferred method.* In a typical run the mixed fatty acids of *Ximenia caffra* oil (406 g.; $E^{1\%}_{1\,cm.}$ 148·3 at 229 mμ) were crystallised from acetone (10 ml. per g.) at −25°. The soluble fraction (226 g.; $E^{1\%}_{1\,cm.}$ 197 at 229 mμ) in light petroleum (b. p. 40—60°; 5 ml. per g. of acids) was kept at −22° for 5 hours. The insoluble acids (60 g.; $E^{1\%}_{1\,cm.}$ 447 at 229 mμ; neutralisation equiv., 292) were converted into methyl esters and fractionally distilled under high vacuum; the fractions with saponification equivalent 293—294 and $E^{1\%}_{1\,cm.}$ > 450 at 229 mμ were combined and hydrolysed, and the acids recrystallised from acetone and light petroleum (Ligthelm and Schwartz, *loc. cit.*), to give white plates, m. p. 39—40° (corr.); $E^{1\%}_{1\,cm.}$ 583 ± 2 at 229 mμ, $E^{1\%}_{1\,cm.}$ 2·5 at 268 mμ. The overall yield was 4—7% of the total fatty acids, *i.e.*, 15—28% of the ximenynic acid present in the starting material.

(b) *By chromatography* (cf. Swift, Rose, and Jamieson, *loc. cit.*). Alumina (100 g.; Peter Spence, chromatographic grade) was treated with a little water and ethyl acetate and then heated

at 145° for 1 hour. The mixed methyl ximenynate concentrates (1·0560 g.; $E^{1\%}_{1\,cm.}$ 325 at 229 mμ; sap. equiv., 294—295) in light petroleum (10 ml.) were slowly poured on a column of alumina (2 × 30 cm.) and then eluted with solvents as follows: (i) 200 ml. of light petroleum, then (ii) 100 ml., (iii) 60 ml., (iv) 80 ml., (v) 60 ml., (vi) 50 ml. of 5, 10, 10, 10, and 50%, respectively, of ether in light petroleum, (vii) ether, and (viii) benzene–ethanol. The total recovery was 96·2%, most of the material being in eluants (ii)—(iv), and that in eluants (iii) and (iv) having $E^{1\%}_{1\,cm.}$ at 229 mμ = 527 and 523, respectively. With more active alumina, lower recoveries were obtained, and " active " alumina did not give any separation.

In other experiments silica gel (Davison Chemical Corp., Baltimore, U.S.A., " grade through 200 mesh ") and Hyflo Supercel (Johns Mansville, U.S.A.) in a ratio of 80 : 20 was the adsorbent; this (30 g.) was well mixed and activated at 190—200° for 1 hour, then tightly packed in a column (2·4 × 50 cm.) and wetted with light petroleum (60 ml.). The mixed acids (1·0268 g.; $E^{1\%}_{1\,cm.}$ 295 at 229 mμ) were dissolved in light petroleum (10 ml.) and poured on the column, which was then eluted by: (i) 200 ml. of 10% benzene in light petroleum; (ii) 200 ml. of 1% ether in light petroleum; then 100 ml. each of (iii) 2·5%, (iv) 5%, (v) 5%, (vi) 5%, (vii) 10%, (viii) 15% ether in light petroleum, and (ix) ether alone. The weights (mg.) and (in parentheses) values of $E^{1\%}_{1\,cm.}$ at 229 mμ were: (i) 3·8 (—), (ii) 0 (—), (iii) 112·4 (333), (iv) 263·7 (12), (v) 200·2 (358), (vi) 132·4 (540), (vii) 134·7 (506), (viii) 90·7 (549), (ix) 66·5 (350); total recovery, 97%.

(c) *By urea-complex formation.* The methyl esters (10 g.; $E^{1\%}_{1\,cm.}$ 148 at 229 mμ) of *Ximenia caffra* oil and methanol saturated with urea at room temperature (300 ml.) were heated till homogeneous and then left for 3 hours at 31°. The crystals were collected (fraction A), and the filtrate kept overnight at room temperature (15°) to give a second crop (B) of crystals. The filtrate (C) and fractions (A) and (B) were suspended in separate quantities of water containing a little concentrated hydrochloric acid and the aqueous phases were extracted twice with light petroleum. The petroleum solutions were washed with water, the solvent was evaporated, and the residues were dried. The weights and the $E^{1\%}_{1\,cm.}$ values at 229 mμ of the different fractions were:

Fraction	Wt., g.	$E^{1\%}_{1\,cm.}$	% of total ximenynic acid in fraction	Fraction	Wt., g.	$E^{1\%}_{1\,cm.}$	% of total ximenynic acid in fraction
A	5·6	57·1	21·6	C	0·8	279	15·1
B	2·8	277	52·5	Loss	0·8	—	10·8

Esters.—*Methyl ximenynate* was prepared from the acid (20 g.) and isolated in the usual way (Hilditch, " Chemical Constitution of Natural Fats," 2nd edn., J. Wiley and Sons, New York, 1947, p. 474); yield, 21·0 g. (100%), b. p. 148°/0·2 mm., 163—165°/0·4 mm., 172—174°/0·8 mm., n^{25}_{D} 1·4700, d^{25}_{25} 0·9067, $E^{1\%}_{1\,cm.}$ 549·2 at 229 mμ (Found: C, 77·5; H, 11·1%; sap. equiv., 292·9. $C_{19}H_{32}O_2$ requires C, 78·0; H, 11·0%; equiv., 292·4). The ester became yellow in the air, and after 30 minutes had absorbed *ca.* 2% of oxygen (Found: C, 76·45; H, 10·7%).

Ethyl ximenynate, similarly prepared (5·4 g. from 5 g. of acid), had b. p. 168—169°/0·2 mm., n^{25}_{D} 1·4680, $E^{1\%}_{1\,cm.}$ 525 at 229 mμ (Found: C, 78·4; H, 11·2%; sap. equiv., 306·9. $C_{20}H_{34}O_2$ requires C, 78·25; H, 11·25%; equiv., 306·6).

Ximenynamide.—This *amide* formed small yellow nest-like crystals, m. p. 105—105·5° (Found: C, 78·3; H, 11·3. $C_{18}H_{31}ON$ requires C, 77·9; H, 11·3%).

p-*Bromophenacyl Ximenynate.*—The *ester*, recrystallised from alcohol, had m. p. 53·8—54·2° (Found: C, 65·8; H, 7·5. $C_{26}H_{35}O_3Br$ requires C, 65·7; H, 7·4%).

Urea Complexes of Ximenynic Acid and Its Derivatives.—These complexes were prepared essentially as described above, recrystallised from *iso*propyl alcohol, and dried in a vacuum. The $E^{1\%}_{1\,cm.}$ values at 229 mμ were determined (alcoholic solution), and the molar ratio of urea to compound calculated. The results were as follows:

Complex with:	Yield value	$E^{1\%}_{1\,cm.}$ at 229 mμ	M. p.	Mols. urea/mol. compound
Ximenynic acid	1·55	132·0	130·5—131·5°	16·0
Methyl ximenynate	1·0	132·6	133—135	15·2
Ximenynyl alcohol	1·0	150·4	133—135	12·1

Ozonolysis of Ximenynic Acid.—A stream of ozonised oxygen (2·5% of ozone) was passed through a solution of ximenynic acid (3 g.) in glacial acetic acid (20 ml.) for 150 minutes, the solution being kept at 15—20° to reduce loss of acetic acid. To the solution were added zinc dust (6·5 g.) and a trace of water, the whole was refluxed with stirring for 90 minutes, and water was added. The product was filtered off and well washed with ether, the combined

filtrate was washed with water and dried ($CaCl_2$), and the ether removed by distillation through a column. The residue was fractionally distilled to give five fractions: (*a*) b. p. 100—120°/650 mm. (*ca.* 3 g.); (*b*) b. p. 120—123°/650 mm. (*ca.* 2 g.); (*c*) b. p. 123°/650 mm.—60°/20 mm. (0·2 g.); (*d*) b. p. 160—167°/0·5 mm. (*ca.* 0·18 g.); (*e*) b. p. 175°/0·5 mm. (*ca.* 0·5 g.). Fraction (*a*) was chiefly acetic acid. Fraction (*b*) contained heptanaldehyde, which formed a semicarbazone (0·3 g.), m. p. 107—109° after one crystallisation from aqueous alcohol (Found: C, 56·3; H, 10·55. Calc. for $C_8H_{17}ON_3$: C, 56·1; H, 10·05%), the m. p. being undepressed when the material was mixed with an authentic sample, m. p. 108—109°. Fraction (*c*) also contained heptanaldehyde (oxime, m. p. and mixed m. p. 54·5°); (*d*) consisted chiefly of azelaic acid, also obtained (0·4 g.) by recrystallisation of (*e*) from ethyl acetate and *iso*heptane; it had m. p. and mixed m. p. 106—107° (Found: C, 57·7; H, 8·9%; equiv., 96·7. Calc. for $C_9H_{16}O_4$: C, 57·4; H, 8·6%; equiv., 94·1). The mother-liquors from the crystallisation of (*e*) were concentrated and boiled with an excess of semicarbazide to give 15 mg. of semicarbazone, m. p. 141—149°, which after four recrystallisations from aqueous alcohol yielded *ca.* 1 mg., m. p. 158—160° (azelaic semialdehyde semicarbazone has m. p. 162°; Scanlan and Swern, *J. Amer. Chem. Soc.*, 1940, **62**, 2305).

Attempted "Elaidinisation" of Ximenynic Acid.—Ximenynic acid (1·4 g.) was treated by the method of Swern *et al.* (*loc. cit.*) (selenium, 0·007 g.; 200°; 2 hours), but the material isolated was unchanged acid (0·48 g.; m. p. and mixed m. p.).

Attempted Reduction of Ximenynic Acid to the Dienoic Acid.—Methyl ximenynate (1·5 g.), reduced by Adams and Marvel's method (*J. Amer. Chem. Soc.*, 1920, **42**, 310), yielded 1·1 g. of product, $E^{1\%}_{1\,cm.}$ 464 at 229 mμ. Reduction of the acid (41·1 mg.) by use of a poisoned palladium–charcoal catalyst (Isler *et al.*, *loc. cit.*) until one mol. of hydrogen had been absorbed (5 min.) afforded a product with $E^{1\%}_{1\,cm.}$ 232 at 229 mμ. The hydrogenation was thus largely unselective. Since Dr. Isler stated (private communication) that the presence of any acid will destroy the toxicity of the catalyst, an experiment was conducted on ximenynyl alcohol (0·05 g.), a sample of poisoned catalyst being used which was obtained from Messrs. Hoffman–La Roche, Switzerland; after absorption of 1 mol. of hydrogen (5 min.), the product isolated had $E^{1\%}_{1\,cm.}$ 670 at 229 mμ, which indicated that the hydrogenation was still largely unselective.

Iodine Values of Ximenynic Acid and Methyl Ximenynate.—The modified methods described above were used, but in preparing the modified Rosenmund–Kuhnhenn reagent, the acetic acid and bromine were cooled before being mixed, because a reaction took place between them at room temperature; the iodine values found with the different reagents are summarised below:

	Acid	Ester
I.V., calc.	273·6	260·6
I.V., calc. for 2 mols. of halogen	182·5	173·8

Woburn method			Wijs method			Rosenmund–Kuhnhenn method		
Hours	Acid	Ester	Hours	Acid	Ester	Hours	Acid	Ester
1	151·9	140·5	1	130·3	124·8	1	193·3	174·9
2	148·1	137·1	2	131·0	125·5	2	196·6	178·9
10	157·4	141·7	10	129·7	124·5			
24	153·7	142·6	24	127·5	120 5	Bromine-vapour method*		
48	161·0	144·2	48	127·5	124 5	1	187·1	170·3
96	189·2	168·7						

* Data obtained from Dr. F. Hawke, Department of Chemistry, University of the Witwatersrand, Johannesburg.

Alkali Isomerisation of Ximenynic Acid.—This process was carried out according to *J. Amer. Oil Chem. Soc.*, 1949, **26**, 399, except that air was excluded. A weighed quantity of the acid or methyl ester (*ca.* 0·1 g.) and ethylene glycol–potassium hydroxide reagent (10 ml.) were placed in a tube, which was then evacuated, sealed, and heated at 180° ± 0·5° for various times. The tubes were cooled under the tap and opened, the contents quantitatively transferred to 100-ml. volumetric flasks, and the volumes made up with purified 96% alcohol. The absorptions were measured in a Beckman spectrophotometer Model DU, after suitable dilution; the results were:

	$E^{1\%}_{1\,cm.}$ at:				$E^{1\%}_{1\,cm.}$ at:		
Time, min.	229 mμ	234 mμ	268 mμ	Time, min.	229 mμ	234 mμ	268 mμ
25	367	353	432	60	217	235	590

To obtain the free acids, the contents of each tube were poured into 20 ml. of water, the solutions just acidified with concentrated hydrochloric acid, and the acids extracted with light petroleum. After evaporation of the petroleum the residue was dried in a vacuum at 80—100°. The absorption in the ultra-violet region was examined in *cyclo*hexane solution with the results summarised below :

Temp.	Duration of heating (min.)	$E^{1\%}_{1\,cm.}$ at 229 mμ	$E^{1\%}_{1\,cm.}$ at 268 mμ	Temp.	Duration of heating (min.)	$E^{1\,cm.}_{1\%}$ at 229 mμ	$E^{1\,cm.}_{1\%}$ at 268 mμ
180°	0	583	2·5	190°	60	155	450
—	25	376	315	—	90	115	425
—	60	251	388	—	120	98	385
—	90	195	420				
—	120	170	455				

The product isomerised at 180° was reduced with lithium aluminium hydride (Ligthelm, von Rudloff, and Sutton, *loc. cit.*). The reduced material was dried, yielding a product with $E^{1\%}_{1\,cm.}$ 456 at 268 mμ. The isomerised acids were crystallised as follows : The acids from the alkali-isomerisation product were dissolved in light petroleum (10 ml. per g. of acid) and left at 0° for a few hours. A brown oil which separated from the solution was removed, and the solution cooled to −60°, to give a white precipitate which was collected on a cooled Buchner funnel and recrystallised twice from light petroleum at −10°, yielding white crystals, m. p. 60—61°; $E^{1\%}_{1\,cm.}$ 1705 at $\lambda_{max.}$ 268 mμ, $E^{1\%}_{1\,cm.}$ 130 at 229 mμ (no maximum). The acid was soluble in dilute alkali and in most organic solvents; it oxidised very rapidly in air with formation of an oil.

Glycerol, Pentaerythritol, and Inositol Esters of Ximenynic Acid.—These esters were prepared according to Wheeler, Riemenschneider, and Sando's method (*J. Biol. Chem.*, 1940, **132**, 687). A weighed quantity of the alcohol (0·3 g.), a slight excess over 1 equiv. of ximenynic acid, and toluene-*p*-sulphonic acid (0·05 g.) were placed in 12″ × 1″ test-tubes, and the tubes evacuated to 0·05 mm. and heated until evolution of gas ceased. The glycerol, pentaerythritol, and inositol esters formed at 150°, 200—220°, and 250°, respectively. After the reaction was completed, the tubes were cooled, the contents dissolved in light petroleum (b. p. 40—60°) or ether, and the solutions washed with 5% potassium carbonate solution; the solvents were then removed. The residual material was taken up in a small volume of mineral turpentine, a few drops of drier (containing 0·5% Pb, 0·05% Co, and 0·03% Mn) added, and the films spread on glass plates and regularly tested for drying (touched with the finger). The inositol, pentaerythritol, and glycerol esters set after about 10, 15, and 20 hours, respectively. All the films, however, after 48 hours' exposure still had a pronounced " after tack," which was only lost after exposure to direct sunlight. After a few weeks the original solutions separated into two phases.

This paper is published with the permission of the South African Council for Scientific and Industrial Research. The authors thank Dr. W. S. Rapson for his interest in the work, Dr. D. A. Sutton, who suggested and carried out the ozonolysis of ximenynic acid, and Messrs. D. J. S. Gray and F. W. Schoening, who carried out the elementary analyses.

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194. *A Synthesis of Vitamin A from* cyclo*Hexanone.*

By J. Attenburrow, A. F. B. Cameron, J. H. Chapman, R. M. Evans, B. A. Hems, A. B. A. Jansen, and T. Walker.

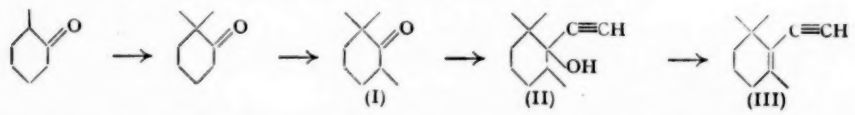
8 : 9-Dehydrovitamin A has been prepared by two routes (cf. Heilbron, *J.*, 1948, 386; 1949, 2031), and by a modification of the scheme vitamin A itself was also synthesised by two routes.

2-Ethynyl-1 : 3 : 3-trimethyl*cyclo*hex-1-ene (III) and 6-methylocta-3 : 5 : 7-trien-2-one are coupled together by Grignard reaction and the tertiary alcohol (XI) so obtained rearranges to give 8 : 9-dehydrovitamin A (IX). Condensation of ethynyl-2 : 6 : 6-trimethyl*cyclo*hex-1-ene (III) with crotonylideneacetone, rearrangement, and oxidation give the 7 : 8-dehydro-C_{18} ketone (VI), which is converted into the same dehydrovitamin A by condensation with ethyl bromoacetate, followed by dehydration and reduction of the ethyl ester of 8 : 9-dehydrovitamin A acid (VIII; R = Et) with lithium aluminium hydride.

1-Ethynyl-2 : 2 : 6-trimethyl*cyclo*hexanol (II) condenses with crotonylideneacetone and with 6-methylocta-3 : 5 : 7-trien-2-one to give C_{18} and C_{20} glycols, (XII) and (XVIII), respectively, in which compounds, after rearrangement, the triple bond is selectively semi-reduced with lithium aluminium hydride. Dehydration of the reduced C_{20} glycol monoacetate (XXII; R = Ac) gives vitamin A acetate, and oxidation of the reduced C_{18} glycol (XX) with subsequent dehydration gives the known C_{18} ketone, which is converted into vitamin A by one of the published methods. The C_{18} acetylenic glycol (XIV) is alternatively obtained by condensation of 2 : 2 : 6-trimethyl*cyclo*hexanone with a C_9 acetylenic alcohol (XIII).

Several syntheses of vitamin A have now been described and excellent reviews of previous work are available (Milas, *Recent Advances in Vitamins and Hormones*, 1947, **5**, 1; Heilbron, *J.*, 1948, 386; Isler, *Chimia*, 1950, **4**, 103; Johnson, *Ann. Reports*, 1949, **46**, 168). It will be noted that all the syntheses described are from β-ionone, which has 13 of the 20 carbon atoms of vitamin A already correctly disposed. It has, however, certain obvious disadvantages as a starting material for the preparation of vitamin A, and Heilbron (*loc. cit.*) has suggested several possible routes for the synthesis of vitamin A and its lower homologues from *cyclo*hexanone, and has prepared several analogues by this method (Heilbron *et al.*, *J.*, 1949, 287, 742, 2023, 3120, 3123; 1950, 633). It was the object of our work to effect a synthesis of vitamin A itself from *cyclo*hexanone by one such route.

The key condensation of the routes outlined by Heilbron is of an ethynyl*cyclo*hexene with a C_7 or C_9 ketone, leading (with a trimethyl-substituted ring) to a C_{18} or C_{20} skeleton; several routes from the C_{18} to the C_{20} skeleton are now well substantiated (Arens and van Dorp, *Rec. Trav. chim.*, 1946, **65**, 338; 1949, **68**, 604; Schwarzkopf, Cahnmann, Lewis, Swidinsky, and Wuest, *Helv. Chim. Acta*, 1949, **32**, 443). 2-Methyl*cyclo*hexanone is available commercially and was selected as starting material. From this point the route envisaged to the ethynyltrimethyl*cyclo*hexene (III) was as follows:



(I) (II) (III)

The methylation of *cyclo*hexanone had been examined previously (Cornubert and Haller, *Bull. Soc. chim.*, 1927, **41**, 367, 894; Colonge and Duroux, *ibid.*, 1940, **7**, 459; Adamson, Marlow, and Simonsen, *J.*, 1938, 774; Fischer and Wunderlich, *Ber.*, 1941, **74**, 1544), and the published method of methylation with methyl iodide and sodamide in a non-polar solvent was found suitable. The methylation was carried out in two stages, the separation of homologues at each stage being effected by fractionation through an 80-plate column with a gauze packing (Dixon, *J. Soc. Chem. Ind.*, 1949, **68**, 88). The earlier method of

separation by fractional crystallisation of the semicarbazones was rejected as practicable only for small samples of the pure ketones.

It may be noted that the m. p. of 2 : 2 : 6-trimethyl*cyclo*hexanone semicarbazone, 209—211°, was found to be lower than those previously recorded, 220—221° (Masson, *Compt. rend.*, 1912, **154**, 517) and 214—216° (Cornubert and Haller, *loc. cit.*). However, repeated recrystallisation did not raise the m. p. and solubility analysis did not indicate the presence of any substantial amount of impurity.

The physical constants of the homologous ketones are shown in Table 1, the m. p.s having been newly determined. It will be seen that methods for analysing mixtures of the

TABLE 1. *Physical properties of methylated* cyclo*hexanones.*

Substituent	B. p.	M. p.	n_D^{20}	d_4^{20}
None	155°	−40·5°	1·4507	0·9478
2-Methyl	166	−14·4	1·4456	0·9250
2 : 2-Dimethyl	173	−20·5	1·4486	0·9145
2 : 6-Dimethyl	170—173	—	1·4508 *	0·9146 *
2 : 2 : 6-Trimethyl	178	−31·8	1·4493 *	0·9043 *
2 : 2 : 6 : 6-Tetramethyl	185	+11·2	1·4470	0·8923

* Both physical properties relate to 18°, not 20°.

ketones based on the measurement of physical constants are largely precluded by the small range of these constants. However, a method of limited applicability was developed, based on the measurement of setting-points. By this means it was possible to determine the composition of mixtures of 2 : 2-dimethyl-, 2 : 2 : 6-trimethyl-, and 2 : 2 : 6 : 6-tetramethyl-*cyclo*hexanones with an accuracy of ± *ca.* 0·5%, provided that the trimethyl compound accounted for more than 85% of the mixture. Preliminary experiments have indicated that a more complete solution of the problem is to be found in the determination of infra-red absorption spectra.

By adding the trimethyl ketone (I) to a solution of sodium acetylide in liquid ammonia, 1-ethynyl-2 : 2 : 6-trimethyl*cyclo*hexanol (II) was readily obtained in high yield. This condensation has now been carried out with both *cyclo*hexanone (Heilbron, Jones, and Richardson, *J.*, 1949, 287) and its 2 : 2 : 6-trimethyl homologue (Milas, MacDonald, and Black, *J. Amer. Chem. Soc.*, 1948, **70**, 1829).

Dehydration of the alcohol (II) to 2-ethynyl-1 : 3 : 3-trimethyl*cyclo*hex-1-ene (III) proved to be difficult. After many attempts to effect it directly had given small or erratic yields of the required hydrocarbon, this was obtained in moderate yield by pyrolysis of its acetate. The acetate and other esters were prepared by treating (II) with one equivalent of ethylmagnesium bromide and reaction of the product with the appropriate acid anhydride (Houben, *Ber.*, 1906, **39**, 1736). The acetate was subsequently prepared by other acetylation procedures, of which the one preferred is given on p. 1102 : methods involving the use of pyridine were not satisfactory. The acetate was best pyrolysed in silicone oil in the presence of zinc oxide, whereupon it gave a 36% yield of hydrocarbon (III). Inferior yields were obtained in the absence of a solvent and substitution of the propionate, *n*-hexanoate, or benzoate for the acetate gave rather smaller yields. The use of zinc, iron, lead monoxide, lead dioxide, ferric oxide, sodium acetate, or lead acetate as catalyst gave a smaller yield of hydrocarbon (III) (10—25%). Silver, copper, magnesium, aluminium, tin, nickel, cobalt, manganese, molybdenum, or tungsten, the oxides of copper, magnesium, calcium, barium, mercuric, aluminium, or bismuth, and manganese dioxide or calcium hydroxide gave very small yields (0—10%).

The resulting product gave the correct analysis and had the ultra-violet absorption to be expected for such a compound. On ozonolysis it gave a 25% yield of geronic acid. Its physical constants agreed with those given by Sobotka and Chanley (*J. Amer. Chem. Soc.*, 1949, **71**, 4136) but not with those by Milas, MacDonald, and Black (*loc. cit.*). Moreover, we had earlier (B.P. 627 453/47) obtained the same compound by direct pyrolysis of the alcohol (II) over aluminium phosphate, as described by Milas (*loc. cit.*) and Heilbron, Jones, and Richardson (*loc. cit.*). This method gave very variable yields, as has also been

noted by Sobotka and Chanley (*loc. cit.*). We were also able to repeat the method used by these authors and obtained identical material.

The acetylenic compound (III) was converted into its Grignard derivative and condensed with crotonylideneacetone (of which an improved preparation is described, p. 1103) to give the tertiary alcohol (IV).

The data for the light absorption of this and the other C_{18} and C_{20} compounds described are collected in Table 2.

TABLE 2.

	$\lambda_{max.}$, Å	$\epsilon_{max.}$		$\lambda_{max.}$, Å	$\epsilon_{max.}$
IV	2300	30 000	XVI	3160	4 300
V	3010	21 000		2660	24 200
	2260	12 600		Infl. 2930—3045	4 400
	Infl. 3110—3120	16 400	XVII	3385	15 000
VI	3400	23 300		2630	9 850
	2440	11 200	XVIII	2810	31 600
VII	3000	25 600		2700	40 600
	2250	17 000	XIX	3170 *	39 400
VIII	3510	33 600		3020 *	47 600
	2650	12 200		2260 *	8 350
IX	3280	35 000		Infl. 2870—2960 *	35 650
	2520	19 400	XX	2850	22 400
XI	2810	36 000		2740	28 200
	2710	34 600		2650	23 400
	Infl. 2350—2450	17 800	XXI	3110	29 400
XII	2290	25 000		2280	8 000
XIV	2800	23 600	XXII	3230 *	46 600
	2690	32 300		3070 *	58 000
XV	3050	25 000		2960 *	43 500
	2400	3 400		2300 *	5 700
	3130 *	25 400			
	2510 *	3 500			

	$\lambda_{max.}$, Å	$\epsilon_{max.}$
† R·CH:CH·CMe:CH·CH:CH·COMe	3310	30 000
	3450 *	25 500
† R·CH:CH·CMe:CH·CH:CH·CMe:CH·CH_2·OH	3250	50 000

* Determination carried out in ethanol. The remaining determinations were made in *n*-hexane.
† R as in Table 3.

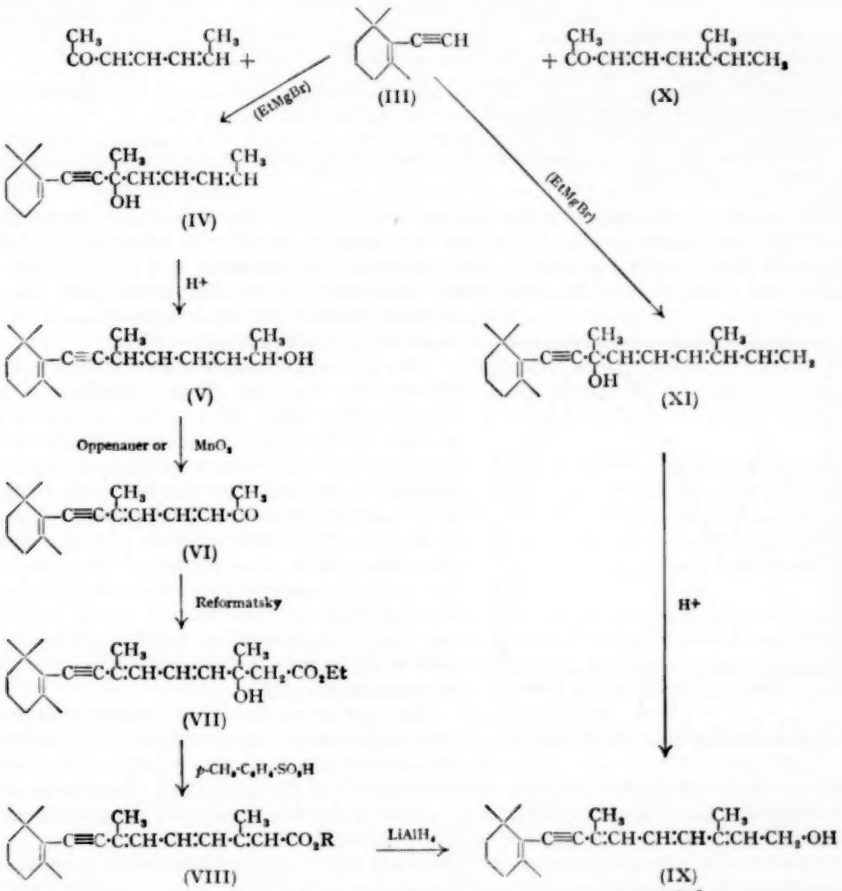
When shaken in ethereal solution with 0·5% sulphuric acid, (IV) underwent rearrangement to give the secondary alcohol (V) in 60% yield. Total hydrogenation of this compound gave the saturated 6-methyl-8-(2 : 2 : 6-trimethyl*cyclo*hexyl)octan-2-ol which was oxidised to the corresponding known ketone (semicarbazone) (Karrer and Morf, *Helv. Chim. Acta*, 1933, **16**, 625).

For the Reformatsky reaction required to complete the C_{20} skeleton it was necessary to oxidise the alcohol (V) to the corresponding ketone (VI); this was effected by Oppenauer oxidation, followed by isolation as the semicarbazone and regeneration, or directly in 80% yield by oxidation with manganese dioxide in light petroleum. The ketone (VI) gave the above saturated ketone (semicarbazone) on total hydrogenation.

Manganese dioxide had previously been used by Ball, Goodwin, and Morton (*Biochem. J.*, 1948, **42**, 516) for the oxidation of vitamin A to retinene; 2-β-ionylidene-ethanol (Wendler, Slates, and Tishler, *J. Amer. Chem. Soc.*, 1949, **71**, 3267) and vitamin A_2 (Henbest and Jones, *Chem. and Ind.*, 1951, 49) have recently been oxidised to the corresponding aldehydes in the same way. In this work five successful oxidations with manganese dioxide are described, and we have also tested the method, with positive results, on simpler alcohols, *i.e.*, allyl alcohol, cinnamyl alcohol, oct-3-yn-2-ol, and 3-dehydro-β-ionol. It therefore appears that the method may be general for alcohols of the allylic type, whether they are primary or secondary and possibly when the unsaturation is acetylenic. Of acetylenic alcohols three were successfully oxidised in this way; a fourth, hex-1-yn-3-ol, was recovered unchanged after treatment with manganese dioxide: it may be significant that this was the only one of the four having acetylenic hydrogen.

The reaction conditions have been examined in some detail and it has been found possible

to prepare precipitated manganese dioxide by means of which a substantially complete oxidation can be effected in ½—1 hour at room temperature, in contrast with the 6—10 days used by Morton and his colleagues. Normal commercial samples of precipitated manganese dioxide commonly have a much lower activity and are often inactive. In the preparation of active material (see p. 1104), it has been found essential to precipitate it in the presence of alkali, or to treat it with alkali after precipitation and before drying. The latter process is also critical and both under- and over-drying can profoundly reduce the activity of the oxide. The active material is a hydrated oxide and of a chocolate-brown colour.



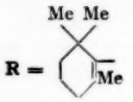
The ketone (VI) obtained by this method was subjected to a Reformatsky reaction to give an ester (VII). On dehydration this gave the oily ester (VIII; R = Et), which on hydrolysis gave the corresponding acid (VIII; R = H) as a crystalline solid, m. p. 161°. The acid showed only slight vitamin A activity; the results of animal-growth tests on this and other compounds described in this paper are collected in Table 3.

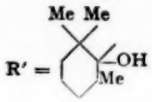
The ester (VIII; R = Et) was reduced to 8 : 9-dehydrovitamin A (IX) with lithium aluminium hydride, as described by Schwarzkopf *et al.* (*loc. cit.*) for vitamin A itself.

The crude (70%) dehydrovitamin thus obtained was, after chromatography, converted into the anthraquinone-2-carboxylate, which, like that of vitamin A, crystallised in two modifications, yellow needles, m. p. 113°, and red needles, m. p. 137°. However, in this

instance the red form was the stable one; the yellow form was stable when dry but changed to the red on contact with acetone. On hydrolysis, 8 : 9-dehydrovitamin A was obtained as a crystalline solid, m. p. 47—50° (*p*-phenylazobenzoate).

TABLE 3.



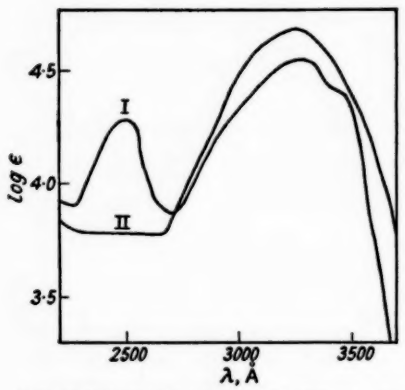


Compound	Activity, as a percentage of that of vitamin A
R·C:C·CMe:CH·CH:CH·CMe:CH·CO_2Et	5
R·C:C·CMe:CH·CH:CH·CMe:CH·CO_2H	0·5—1
R·C:C·CMe(OH)·CH:CH·CH:CMe·CH:CH_2	4
R·C:C·CMe:CH·CH:CH·CMe:CH·CH_2·OH	40 *
R'·C:C·CMe:CH·CH:CH·CMe:CH·CH_2·OH	1
R'C:C·CMe:CH·CH:CH·CMe:CH·CH_2·OAc	1

* This figure has been calculated from the results of tests carried out with the anthraquinone-2-carboxylate (yellow form).

On a column of alumina the dehydrovitamin A showed a blue fluorescence under ultra-violet radiation, similar to that shown by the vitamin. It differed from the vitamin in giving, with the Carr–Price reagent, a blue colour that rapidly faded to a stable purple.

A second route to the dehydrovitamin employed ketone (X), which gave the C_{20} tertiary alcohol (XI) on condensation with the same acetylenic hydrocarbon (III).



I, 8 : 9-*Dehydrovitamin A*. II, *Vitamin A*.

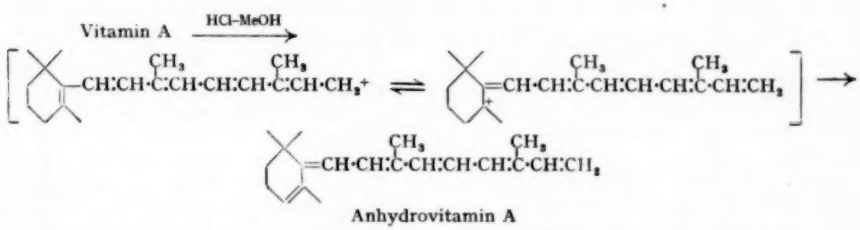
The ketone (X) was prepared by the route of Cheeseman, Heilbron, Jones, Sondheimer, and Weedon (*J.*, 1949, 2031), but it was found possible to substitute calcium for lithium in the ethynylation of crotonylideneacetone, and the rearranged condensation product was oxidised by manganese dioxide in light petroleum, instead of by the Oppenauer method, giving a better conversion and a purer product. The use of the less pure ketone obtained by the Oppenauer oxidation led to complex mixtures, which it was found impossible to purify sufficiently to yield a crystalline anthraquinone-2-carboxylate after rearrangement.

The crude condensation product (XI) was, after purification by chromatography and distillation, rearranged in a homogeneous acidic medium to give a mixture containing dehydrovitamin A (60% of IX). Chromatography of the mixture gave a product (75% of IX) that yielded a crystalline anthraquinone-2-carboxylate, identical in all respects with that previously obtained.

The ultra-violet absorption curves for vitamin A and 8 : 9-dehydrovitamin A are shown for comparison in the figure.

8 : 9-Dehydrovitamin A differs markedly from vitamin A in its ease of dehydration. Whereas vitamin A is well known to be readily dehydrated by, *e.g.*, methanolic hydrogen chloride, yet the dehydrovitamin when treated with this reagent retained its ultra-violet absorption maximum at 325 mμ and no absorption at longer wave-lengths appeared. The triple bond clearly exerts a stabilising effect, and this fact strengthens the case for a formulation of anhydrovitamin A involving a shift of the whole conjugated system during the dehydration, as opposed to formulations involving changes in only the first four carbon atoms of the side chain (Meunier, Dulou, and Vinet, *Bull. Soc. Chim. biol.*, 1942, **25**, 371; *Compt. rend.*, 1943, **216**, 907; Shantz, Cawley, and Embree, *J. Amer. Chem. Soc.*, 1943, **65**, 901). The presence of the triple bond in the conjugated system would be expected to make

the contribution of the " rearranged " form of the carbonium ion very small and thus for 8 : 9-dehydrovitamin A to render largely inoperative the mechanism suggested by Meunier *et al.*



Anhydrovitamin A

Animal tests on the anthraquinone 2-carboxylate of 8 : 9-dehydrovitamin A showed the activity of the free alcohol to be 40% of that of vitamin A. Tests on the free 8 : 9-dehydrovitamin showed its activity to be only 10% of that of vitamin A, but under the conditions of the tests this is likely to have been due to decomposition of the samples. It can, therefore, only be asserted that its activity lies between 10 and 40% of that of vitamin A, but it is thus considerably more active than any other analogue yet prepared.

The considerable difficulties encountered in the dehydration of the alcohol (II) to the hydrocarbon (III) had prompted the suggestion that this might more readily be accomplished if the unsaturated side-chain was first built up by condensation with the carbinol (II) : in fact it was found that the desired effect was produced even by a saturated side-chain, and 1-hex-1′-yn-1′-yl-2 : 2 : 6-trimethyl*cyclo*hexanol, prepared by condensing hex-1-yne and 2 : 2 : 6-trimethyl*cyclo*hexanone (I), was dehydrated to 2-hex-1′-yn-1′-yl-1 : 3 : 3-trimethyl*cyclo*hex-1-ene by aqueous sulphuric acid, acetic anhydride containing a trace of sulphuric acid, boiling acetic anhydride, or several other reagents, of which none had effected the dehydration of (II) to (III).

Accordingly, a Grignard compound was prepared by the addition of the alcohol (II) to two mols. of ethylmagnesium bromide in ether and was treated with crotonylideneacetone to give the glycol (XII), which was rearranged under the usual homogeneous conditions to give a second C_{18} glycol (XIV). This compound was also obtained by condensation of the Grignard derivative of 6-methylocta-3 : 5-dien-7-yn-2-ol (XIII) (Cheeseman *et al., loc. cit.*) with 2 : 2 : 6-trimethyl*cyclo*hexanone (I).

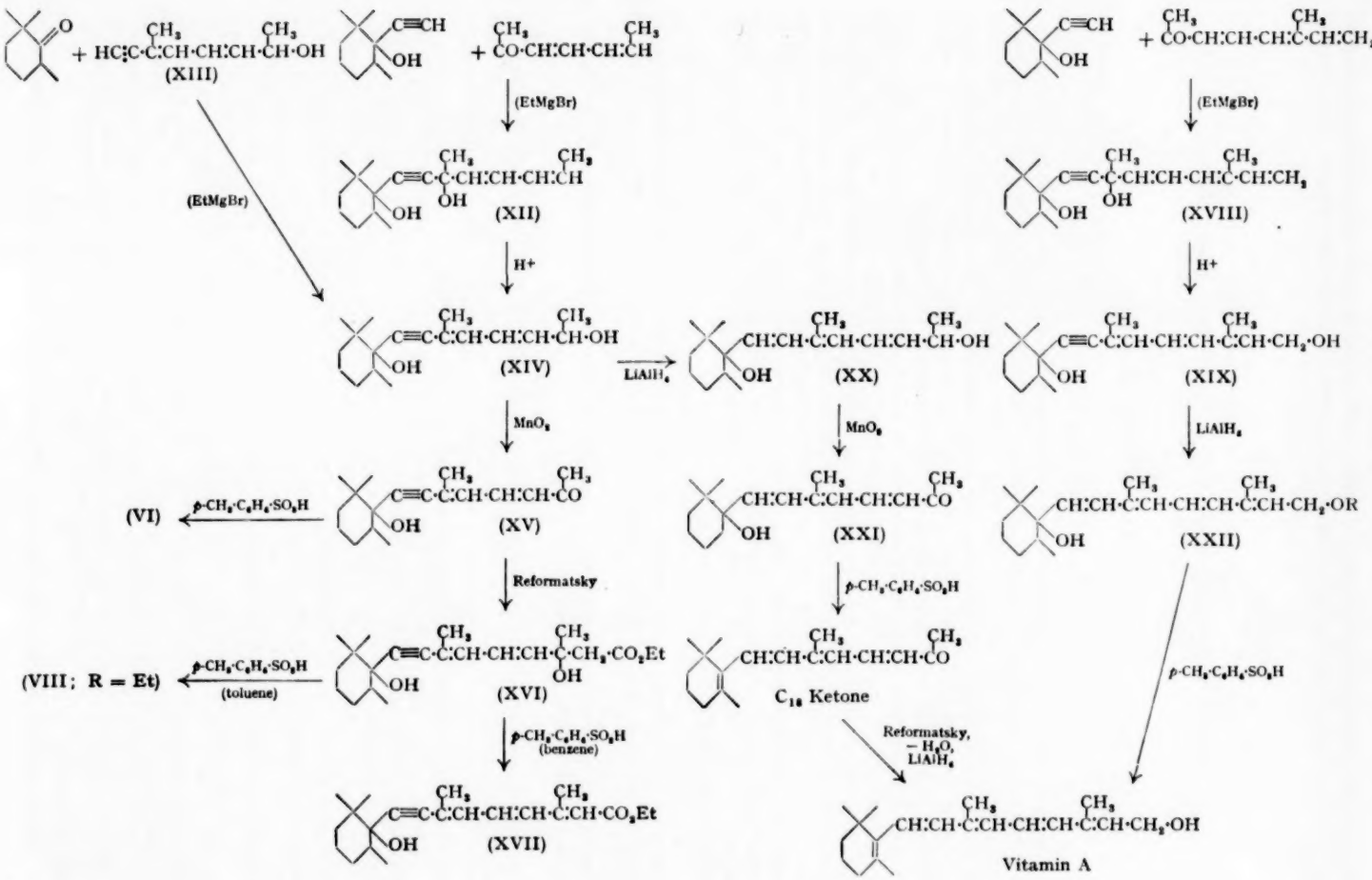
The acetylenic alcohol (XIII) has also been oxidised with manganese dioxide to the corresponding ketone (semicarbazone). Both the alcohol and the ketone show considerable instability : the former has been distilled on many occasions, but occasionally polymerised explosively during the process; the latter cannot be heated above room temperature without vigorous decomposition occurring and has not been distilled.

Glycol (XIV) was oxidised to the corresponding ketone (XV) (semicarbazone; 2 : 4-dinitrophenylhydrazone) with manganese dioxide, and (XV) was readily dehydrated, preferably by toluene-*p*-sulphonic acid in boiling toluene, to the 7 : 8-dehydro-C_{18} ketone (VI).

The hydroxy-ketone (XV) was subjected to a Reformatsky reaction and gave with two molecular proportions of ethyl bromoacetate the glycol-ester (XVI). Dehydration of this substance with toluene-*p*-sulphonic acid in boiling benzene gave a hydroxy-ester, which, on the basis of its light absorption, had formula (XVII), whereas the same reagent in boiling toluene gave the 8 : 9-dehydrovitamin A ester (VIII; R = Et) previously obtained.

Similarly, the di-Grignard complex from 1-ethynyl-2 : 2 : 6-trimethyl*cyclo*hexanol (II), in this instance in benzene, was condensed with 6-methylocta-3 : 5 : 7-trien-2-one (X) to give the ditertiary glycol (XVIII); this, under homogeneous acidic conditions, rearranged to give a crystalline glycol (XIX). The crystalline material was first obtained by regeneration from its anthraquinone-2-carboxylate, but later directly from the reaction product. It gave a green colour with the Carr–Price reagent and had only slight vitamin A activity. Neither it nor its anthraquinone-2-carboxylate has been dehydrated to 8 : 9-dehydrovitamin A.

The acetylenic alcohol (II) has also been condensed, by the same procedure, with


(XIII)
(EtMgBr)
(XII)
H+
(XIV)
LiAlH4
(XX)
(XIX)
MnO2
(XV)
(XXI)
(XXII)
LiAlH4
p-CH3·C6H4·SO3H
(VI)
Reformatsky
(XVI)
(VIII; R = Et)
(toluene)
(benzene)
(XVII)
C18 Ketone
Reformatsky, − H2O, LiAlH4
Vitamin A

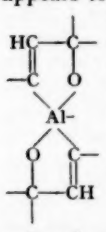
acetaldehyde, and with acetic anhydride at −70° to give 4-(1-hydroxy-2 : 2 : 6-trimethyl-*cyclo*hexyl)but-3-yn-2-ol (3 : 5-dinitrobenzoate) and 4-(1-hydroxy-2 : 2 : 6-trimethyl*cyclo*-hexyl)but-3-yn-2-one, respectively, compounds analogous to the 3-dehydro-β-ionol and -ionone recently described by Sobotka and Chanley (*J. Amer. Chem. Soc.*, 1949, **71**, 4136). The hydroxy-ketone was also prepared from the glycol in good yield by oxidation with manganese dioxide.

The outstanding problem remaining in the synthesis of vitamin A itself was the semi-reduction of the triple bond. Many attempts had been made in the *cyclo*hexene serias and more were made in the *cyclo*hexanol series: a considerable hindrance was the difficulty of determining whether any reduction occurring was selective. Attempts to analyse reduction products by the preparation and separation of derivatives were unsuccessful, and vitamin A activity tests were precluded by the comparatively high activity of the 8 : 9-dehydrovitamin. Certain colour reactions were also examined, but the acetylenic compounds and the corresponding ethylenic compounds gave very similar colours. In fact, in the early part of this work the only useful criteria available were measurements of unsaturation by total hydrogenation and of ultra-violet absorption spectra.

Triple carbon–carbon linkages in otherwise saturated systems have been shown to exhibit an absorption band in the infra-red between 2100 and 2240 cm.$^{-1}$ (Wotiz and Miller, *J. Amer. Chem. Soc.*, 1949, **71**, 3441); the band showed greatest intensity when the triple bond was near the end of the chain and weakened rapidly as it moved towards the centre of the molecule. No previous examination of a polyenyne system has been reported. However, an examination of the infra-red absorption of a series of pairs consisting of an acetylenic compound and the corresponding ethylenic compound [3-methylocta-4 : 6-dien-1-yn-3-ol and 3-methylocta-1 : 4 : 6-trien-3-ol; 6-methylocta-3 : 5-dien-7-yn-2-ol (XIII) and 6-methylocta-3 : 5 : 7-trien-2-ol; acetylenic ketone (VI) and C_{18} ketone semicarbazones; 3-dehydro-β-ionone and β-ionone semicarbazones] showed the acetylenic compounds all to have at 2100—2240 cm.$^{-1}$ a well-defined band which was entirely absent from the ethylenic compounds. Thus a comparison of the intensity of this band before and after an attempted semi-reduction, taken in conjunction with the ultra-violet absorption (and total hydrogenation figures, when necessary) gave a satisfactory measure of the extent of selective semi-reduction achieved.

Sobotka and Chanley (*J. Amer. Chem. Soc.*, 1949, **71**, 4140) had recently announced the selective semi-reduction of the triple bond in *cyclo*hex-1-en-1-ylethynylmethylcarbinol with lithium aluminium hydride, but when applied to our compounds this reagent did not reduce the triple bond selectively in either the analogous alcohol (IV) or the alcohol (V). It did so, however, when applied in the *cyclo*hexanol series to the glycols (XIV and XIX).

Thus a hydroxyl group in the allyl position with respect to the acetylenic linkage appears to be necessary for its reduction, and the mechanism may well be that suggested by Hochstein and Brown (*J. Amer. Chem. Soc.*, 1948, **70**, 3484) in the reduction of cinnamyl alcohol to dihydrocinnamyl alcohol, involving a cyclic intermediate, in our examples of the type inset. The unsaturated linkage in the groups >C(OH)·C:C· appears to be reduced preferentially to that in the groupings −CH:CH·CH(OH)·CH_3 and >C:CH·CH_2·OH, *e.g.*, in glycols (XIV) and (XIX), respectively, but total hydrogenation and ultra-violet spectroscopy indicated that in the alcohol (IV), containing the grouping −C:C·C(CH_3)(OH)·CH:CH·, the double bond was preferentially reduced.



In the reduction of the C_{18} acetylenic glycol (XIV) it was found that over-reduced material could be separated chromatographically, and the mixture containing the triene glycol (XX), thus purified, was oxidised with manganese dioxide to give a hydroxy-ketone (XXI), which was dehydrated with toluene-*p*-sulphonic acid in boiling toluene. From the mixture obtained after chromatography the known C_{18} ketone was isolated as its semicarbazone. Its identity was confirmed by m. p., mixed m. p., ultra-violet absorption spectrum, and finally, by conversion into vitamin A by the method of Schwarzkopf *et al.* (*loc. cit.*).

The C_{20} glycol (XIX) on reduction with lithium aluminium hydride gave a crystalline

polyene glycol (XXII; R = H). This glycol was found to occur in two forms, m. p. 79° and 120°, the former being considerably less stable. It was isolated from the reaction mixture only occasionally and was readily converted into the high-melting form on attempted recrystallisation; it also absorbed atmospheric oxygen more rapidly. Acetylation of either form under very mild conditions gave one monoacetate only (XXII; R = Ac), and this on mild hydrolysis gave the higher-melting isomer. It seems probable that the two forms are related as *cis-trans*-isomers about the newly formed double bond.

Dehydration of the monoacetate (XXII; R = Ac) with toluene-*p*-sulphonic acid in toluene at 80°, boiling benzene, or chloroform gave a mixture of vitamin A acetate (50%), unchanged starting material, and anhydrovitamin A. Chromatography readily separated unchanged starting material from the other components, giving a mixture containing about 80% of vitamin A acetate from which crystalline vitamin A anthraquinone-2-carboxylate was readily obtained. Its identity was confirmed by m. p., mixed m. p., ultra-violet absorption, and animal-growth tests.

Experimental

All experiments were carried out in a nitrogen atmosphere and products were generally stabilised by the addition of small quantities of quinol or α-tocopherol. Active hydrogen was determined by Zerewitinoff's method, and unsaturation by use of platinum oxide in acetic acid, unless otherwise specified.

2-Ethynyl-1 : 3 : 3-trimethylcyclohex-1-ene (III).—(A) 1-Ethynyl-2 : 2 : 6-trimethylcyclohexanol (150 g.) was distilled slowly (*ca.* 25 g./hour) at 130—140° (bath-temp.)/30 mm. through a glass tube (70 cm. × 2 cm.) containing a supported aluminium phosphate catalyst (Heilbron, Jones, and Richardson, *J.*, 1949, 287) kept at 300—310°. The emergent gases were condensed by a water-condenser and collected in a flask equipped with a solid carbon dioxide–acetone trap. Ether (100 ml.) was added to the pyrolysis product, and the ethereal extract separated, dried ($CaCl_2$), and evaporated. Fractional distillation gave the crude dehydration product (34 g.), b. p. 66—70°/18 mm., n_D^{18} 1·491. This was added to an ethanolic solution of silver nitrate (10%; 75 ml.) and kept overnight. The precipitated silver salt was filtered off, washed with alcohol and water, and refluxed with a solution of potassium cyanide (70 g.) in water (200 ml.), and the mixture steam-distilled. The distillate was extracted with ether, and the ethereal extract dried ($CaCl_2$) and evaporated. Distillation of the residue gave 2-ethynyl-1 : 3 : 3-trimethylcyclohex-1-ene as a colourless liquid (20 g.), b. p. 68—69°/18 mm., n_D^{14} 1·4925 (Milas, MacDonald, and Black, *J. Amer. Chem. Soc.*, 1948, **70**, 1829, give b. p. 56—57°/18 mm., n_D^{25} 1·4745; Sobotka and Chanley, *ibid.*, 1949, **71**, 4136, give b. p. 69—70°/13 mm., n_D^{20} 1·4915) (Found: C, 88·9; H, 10·8. Calc. for $C_{11}H_{16}$: C, 89·2; H, 10·8%). Active H: 1·0. Unsaturation: 2·9, 3·2|=. Light absorption (in *n*-hexane): Maximum at 2270 Å, ε 13 000 (Sobotka and Chanley, *loc. cit.*, give $\lambda_{max.}$ 2270 Å, ε 13 000).

1-Ethynyl-2 : 2 : 6-trimethylcyclohexyl acetate. (i) 1-Ethynyl-2 : 2 : 6-trimethylcyclohexanol (73 g.) was added to a stirred solution of ethylmagnesium bromide (1 mol.; determined by titration of an aliquot with standard acid) in ether (*ca.* 400 ml.) which was kept at −5°. The stirring was continued for a further 30 minutes at 0°, and the mixture refluxed for 1 hour. It was cooled to −5°, and acetic anhydride (90 g., 2 mols.) in ether (150 ml.) added. Stirring was continued at −5° for 2 hours and at room temperature overnight. The mixture was poured into 2N-sulphuric acid, and the product isolated with ether. Removal of the solvent gave a solid which was recrystallised from ethanol, giving *1-ethynyl-2 : 2 : 6-trimethylcyclohexyl acetate* (64 g., 70%), m. p. 57·5—58·5° (Found: C, 74·95; H, 9·65; OAc, 27·9. $C_{11}H_{17}$·OAc requires C, 74·95; H, 9·7; OAc, 28·35%). Active H: 1·09.

(ii) The alcohol (II) (50 g.), acetic anhydride (68 g., 2 mols.), and acetyl bromide (1 ml.) were heated together on a steam-bath for 16 hours. The mixture was poured into water, and the product isolated with light petroleum (b. p. 40—60°). After the removal of solvent the residue crystallised; recrystallisation from ethanol gave the acetate (29·1 g., 46%). From the mother-liquors a liquid (22 g.) was obtained by evaporation, and by adding this to the next preparation the overall yield was raised, after a few cycles, to 60%.

By method (i) the following *1-ethynyl-2 : 2 : 6-trimethylcyclohexyl* esters were obtained by means of the appropriate acid anhydrides: *propionate*, platelets from ethanol, m. p. 43—44°, b. p. 118—128°/12 mm. (Found: C, 75·1; H, 9·7. $C_{14}H_{22}O_2$ requires C, 75·65; H, 9·95%); n-*butyrate*, b. p. 139—141°/12 mm., $n_D^{13·5}$ 1·4802 (Found: C, 76·5; H, 10·55. $C_{15}H_{24}O_2$ requires C, 76·25; H, 10·25%); n-*valerate*, b. p. 78—80°/1 mm., n_D^{14} 1·4730 (Found: C, 77·15; H,

10·25. $C_{16}H_{26}O_2$ requires C, 76·75; H, 10·5%); n-*hexanoate*, b. p. 93—94°/0·03 mm., n_D^{14} 1·4750 (Found: C, 77·4; H, 10·45. $C_{17}H_{28}O_2$ requires C, 77·2; H, 10·7%); *crotonate*, m. p. 40—41°, b. p. 76°/0·04 mm. (Found: C, 76·7; H, 9·25. $C_{15}H_{22}O_2$ requires C, 76·9; H, 9·45%); *benzoate*, m. p. 97—98°, b. p. 164°/13 mm. (Found: C, 79·8; H, 8·0. $C_{18}H_{22}O_2$ requires C, 79·95; H, 8·2%).

(B) 1-Ethynyl-2 : 2 : 6-trimethyl*cyclo*hexyl acetate (25 g.), zinc oxide (5 g., 1 equiv.), and silicone oil (20 ml.; Dow Corning 550) were stirred together vigorously at 160 mm. and heated in an oil-bath to 160—180°, whereupon a liquid began to distil. As the rate of distillation became slower, the bath temperature was gradually raised to 200° and the pressure lowered, finally to 14 mm. The distillate (17 g.) was taken up in light petroleum (b. p. 40—60°), and the solution washed with saturated sodium hydrogen carbonate solution and dried. The product was distilled at 12 mm., and the fraction boiling up to 90° (7·5 g.) collected [light absorption (in *n*-hexane): maximum at 2280 Å; $E_{1\,cm.}^{1\%}$ 815]. Purification through the silver salt gave 2-ethynyl-1 : 3 : 3-trimethyl*cyclo*hex-1-ene (6·5 g., 36%), identical in all respects with that described under (A) above.

Crotonylideneacetone. Crotonaldehyde (2800 ml.) was added during 2 hours to a refluxing suspension of barium hydroxide (octahydrate; 195 g.) in " AnalaR " acetone (7500 ml.), and the mixture stirred for a further 1½ hours without further heating. A solution of 2N-hydrochloric acid (700 ml.) was then added to the cooled mixture, the precipitated barium chloride filtered off, and excess of acetone removed from the filtrate on a steam-bath. The residue was steam-distilled, and the product isolated with ether. After removal of the solvent the residue was fractionated through a 24" Fenske column. A fraction having b. p. 84—86°/22 mm. and n_D^{15} 1·5210—1·5250 was collected (1520 g., 41%).

*3-Methyl-1-(2 : 6 : 6-trimethyl*cyclo*hex-1-en-1-yl)octa-4 : 6-dien-1-yn-3-ol* (IV).—2-Ethynyl-1 : 3 : 3-trimethyl*cyclo*hex-1-ene (14·8 g.) in ether (50 ml.) was added during 30 minutes to a solution of ethylmagnesium bromide (from magnesium, 2·92 g., and ethyl bromide, 16·4 g.) in ether (100 ml.), the temperature being kept between −30° and −40°. After being stirred overnight at room temperature, the solution was cooled to −40° and crotonylideneacetone (13·2 g.) in ether (50 ml.) was added during 30 minutes. The mixture was allowed to warm to room temperature and stirred for a further 90 minutes. A saturated solution of ammonium chloride (50 ml.) diluted with water (50 ml.) was added slowly to the ice-cold mixture, and the ethereal layer separated. After drying ($MgSO_4$), the solvent and unchanged starting material were removed, finally at 1 mm. Distillation of the residue gave *3-methyl-1-(2 : 6 : 6-trimethyl*cyclo*hex-1-en-1-yl)octa-4 : 6-dien-1-yn-3-ol* (18·8 g., 73%), b. p. 110°/10^{-5} mm., n_D^{15} 1·5345 (Found: C, 83·6; H, 10·6. $C_{18}H_{26}O$ requires C, 83·7; H, 10·1%). Active H: 1·1. Unsaturation: 4·5|=. Light absorption: see Table 2.

*6-Methyl-8-(2 : 6 : 6-trimethyl*cyclo*hex-1-en-1-yl)octa-3 : 5-dien-7-yn-2-ol* (V).—The acetylenic alcohol (IV) (19 g.) was dissolved in acetone (500 ml.), and sulphuric acid (3·5 g.) in water (200 ml.) was added. The clear solution was kept at room temperature for 24 hours. Saturated sodium hydrogen carbonate solution (250 ml.) was added, and the product isolated with light petroleum (b. p. 40—60°). After removal of the solvent *in vacuo* the residue was distilled to give the *alcohol* (V) (15·5 g., 60%), as a pale yellow viscous oil, b. p. 100—120°/10^{-5} mm., n_D^{14} 1·5650 (Found: C, 84·1; H, 10·2. $C_{18}H_{26}O$ requires C, 83·7; H, 10·1%). Active H: 1·05. Unsaturation: 4·9|=. Light absorption: see Table 2.

*6-Methyl-8-(2 : 6 : 6-trimethyl*cyclo*hexyl)octan-2-one.*—A solution of the secondary alcohol (V) (1 g.) in glacial acetic acid (15 ml.) was shaken with hydrogen in the presence of Adams's catalyst until absorption ceased. After removal of the catalyst by filtration, the product was oxidised by dropwise addition of a solution of chromic acid (0·5 g.) in acetic acid (5 ml.), and the solution kept overnight at room temperature and then poured into a mixture of ice and sodium hydroxide solution (6·5 g.; in 500 ml.), and the product isolated with ether. Removal of the solvent and distillation gave 6-methyl-8-(2 : 6 : 6-trimethyl*cyclo*hexyl)octan-2-one (0·72 g.) as a colourless liquid, b. p. 110°/0·1 mm., n_D^{15} 1·4696 (Found: C, 81·0; H, 13·0. Calc. for $C_{18}H_{34}O$: C, 81·2; H, 12·9%). The semicarbazone, prepared in the usual manner, crystallised from methanol in colourless cubes, m. p. 119—120° (Found: N, 12·6. Calc. for $C_{19}H_{37}ON_3$: N, 12·9%) (Karrer and Morf, *Helv. Chim. Acta*, 1933, **16**, 625, give m. p. 114°).

*6-Methyl-8-(2 : 6 : 6-trimethyl*cyclo*hex-1-en-1-yl)octa-3 : 5-dien-7-yn-2-one* (VI).—(i) A solution of the secondary alcohol (V) (10 g.) and aluminium *tert.*-butoxide (30 g.) in dry acetone (400 ml.) and dry benzene (600 ml.) was refluxed for 48 hours. The cold solution was poured into 2N-sulphuric acid (1 l.), the mixture shaken, and the organic layer separated, washed with sodium hydrogen carbonate solution and water, and dried. Removal of the solvent and distillation of the residue gave a viscous yellow liquid (7 g.), b. p. 90—100°/10^{-5} mm., n_D^{15} 1·5728;

The crude material was treated with semicarbazide acetate in aqueous methanol and gave a product (4·7 g.), m. p. 192—198°. Further recrystallisation from methanol gave the pure *semicarbazone*, m. p. 204—205° as very fine colourless needles (Found: N, 13·3. $C_{19}H_{27}ON_3$ requires N, 13·4%). Light absorption (in ethanol): maxima at 3420 and 2640 Å, ε 43 500 and 14 200, respectively. Inflection at 3060—3110 Å, ε 21 600.

The semicarbazone (4 g.), 3N-sulphuric acid (150 ml.), and light petroleum (300 ml.; b. p. 80—100°) were refluxed with vigorous stirring for 16 hours. The cooled mixture was filtered from unchanged semicarbazone, and the petroleum layer washed with saturated sodium hydrogen carbonate solution and dried (Na_2SO_4). Removal of the solvent and distillation of the product gave the *ketone* (VI) (1 g.), b. p. 100°/10^{-5} mm., n_D^{14} 1·6022 (Found: C, 84·5; H, 9·7. $C_{18}H_{24}O$ requires C, 84·3; H, 9·4%). Light absorption: see Table 2.

Hydrogenation. The ketone (340 mg.) on hydrogenation in ethyl acetate with platinic oxide catalyst absorbed 170 ml. of hydrogen at 20°/764 mm., equivalent to 5·2 per molecule. Isolation of the product and treatment with semicarbazide acetate gave the semicarbazone of 6-methyl-8-(2 : 6 : 6-trimethyl*cyclo*hexyl)octan-2-one m. p. 118—120° undepressed when the sample was mixed with the specimen described previously.

(ii) A solution of the secondary alcohol (V) (1 g.) in light petroleum (b. p. 40—60°; 50 ml.) was shaken with manganese dioxide (10 g.) for 1 hour. Isolation and distillation gave the ketone (VI) (0·8 g.), n_D^{15} 1·5975. Light absorption (in *n*-hexane): maxima at 3360 and 2430 Å, $E_{1cm.}^{1\%}$ 842 and 440, respectively.

Active Manganese Dioxide.—A solution of manganese sulphate (tetrahydrate; 1110 g.) in water (1500 ml.) and a solution of sodium hydroxide (40%; 1170 ml.) were added simultaneously during 1 hour to a hot stirred solution of potassium permanganate (960 g.) in water (6 l.). Manganese dioxide was precipitated soon after the start as a fine brown solid. Stirring was continued for a further hour and the solid was then collected with a centrifuge and washed with water until the washings were colourless. The solid was dried in an oven at 100—120° and ground to a fine powder (920 g.) before use.

Oxidations with Manganese Dioxide.—Cinnamaldehyde. Cinnamyl alcohol (5 g.) was stirred for 30 minutes with a suspension of manganese dioxide (commercial sample; 50 g.) in carbon tetrachloride (250 ml.). The mixture was filtered and the filtrate evaporated. The residue was dissolved in an aqueous-alcoholic solution of semicarbazide hydrochloride (7·5 g.) and sodium acetate (9 g.), heated to 60°, and then kept at room temperature for 2 hours. The cinnamaldehyde semicarbazone (5 g.), m. p. 212—215° (lit., m. p. 215°), was collected.

Acraldehyde. Allyl alcohol (2 g.) was stirred for 30 minutes with a suspension of manganese dioxide (commercial sample; 20 g.) in light petroleum (b. p. 40—60°; 100 ml.) and the mixture was quickly filtered without suction. The precipitate was washed with solvent and the combined filtrates were added to a solution of Brady's reagent (8 g. of 2 : 4-dinitrophenylhydrazine, 16 ml. of concentrated sulphuric acid, and methanol to a total volume of 200 ml.). Water was added, and red crystalline acraldehyde 2 : 4-dinitrophenylhydrazone (4·7 g.), m. p. 165° (lit., m. p. 165°), separated.

Oct-3-yn-2-one. Oct-3-yn-2-ol (1 g.) (Bowden, Heilbron, Jones, and Weedon, *J.*, 1946, 43) was stirred for 30 minutes with a suspension of manganese dioxide (commercial sample; 10 g.) in light petroleum (b. p. 40—60°; 50 ml.). The mixture was filtered and evaporated, and the residue was treated with semicarbazide hydrochloride in the usual fashion to give the desired semicarbazone (1·45 g.), m. p. 109° (lit., m. p. 109°).

3-Dehydro-β-ionone. 3-Dehydro-β-ionol (0·5 g.) (Sobotka and Chanley, *J. Amer. Chem. Soc.*, 1949, **71**, 4136) in light petroleum (b. p. 40—60°; 25 ml.) was shaken with active manganese dioxide (5 g.) for 1 hour. After removal of the solvent the residue was treated with a 1% solution of 2 : 4-dinitrophenylhydrazine in ethanol containing 1% of hydrochloric acid (50 ml.). The orange crystals deposited (0·36 g.) had m. p. 140—141° undepressed when the sample was mixed with a specimen prepared from 3-dehydro-β-ionone synthesised by another route (Sobotka and Chanley, *loc. cit.*).

*Ethyl 3-Hydroxy-3 : 7-dimethyl-9-(2 : 6 : 6-trimethyl*cyclo*hex-1-en-1-yl)nona-4 : 6-dien-8-yne-1-carboxylate* (VII). The ketone (VI) (6 g.) in benzene (150 ml.) reacted with ethyl bromoacetate (4·1 g.) and activated zinc (1·18 g.) to give a red viscous liquid (7·0 g.), n_D^{15} 1·550. Light absorption (in *n*-hexane): maxima at 3000 and 2250 Å; $E_{1cm.}^{1\%}$ 710 and 448, respectively. Distillation gave the pure *hydroxy-ester*, b. p. 140°/10^{-5} mm., n_D^{14} 1·5490 (Found: C, 76·8; H, 9·3; OEt, 12·2. $C_{20}H_{27}O_2 \cdot OEt$ requires C, 76·7; H, 9·4; OEt, 13·1%). Unsaturation: 4·5. Active H: 1·0. Light absorption: see Table 2.

*Ethyl 3 : 7-Dimethyl-9-(2 : 6 : 6-trimethyl*cyclo*hex-1-en-1-yl)nona-2 : 4 : 6-trien-8-yne-1-carb-*

oxylate (VIII; R = Et).—The hydroxy-ester (VII) (5·7 g.) was refluxed with toluene-*p*-sulphonic (0·05 g.) in benzene (90 ml.) for 4 hours. The solution was washed with saturated sodium hydrogen carbonate solution, dried (Na_2SO_4), and evaporated, to give the crude ester as a dark red liquid (5·0 g.), n_D^{14} 1·610. It was chromatographed on deactivated alumina (Grade III Brockmann) with *n*-hexane as solvent and developer, and gave the *ethyl* ester (VIII; R = Et) as a dark yellow oil (2·8 g.), n_D^{14} 1·622 (Found: C, 81·1; H, 9·4; OEt, 14·2. $C_{29}H_{25}O{\cdot}OEt$ requires C, 80·9; H, 9·3; OEt, 13·8%). Unsaturation: 6·3 $\overline{|}$. Light absorption: see Table 2.

3 : 7-*Dimethyl*-9-(2 : 6 : 6-*trimethyl*cyclo*hex*-1-*en*-1-*yl*)*nona*-2 : 4 : 6-*trien*-8-*yne*-1-*carboxylic Acid* (VIII; R = H).—The ester (VIII; R = Et) (3·0 g.) in alcoholic potassium hydroxide (10%; 100 ml.) was shaken for several hours until solution was complete, and set aside for 5 days. Water (300 ml.) was added, the solution extracted with ether, and the pH of the aqueous portion lowered to 3·0 by addition of phosphoric acid. The emulsion was extracted with ether, and the ethereal extract dried ($MgSO_4$) and evaporated, giving a yellow crystalline solid. Recrystallisation from ether gave the *acid* as fine yellow needles, m. p. 161° (Found: C, 80·6; H, 8·9. $C_{20}H_{26}O_2$ requires C, 80·4; H, 8·8%). Light absorption: see Table 2.

3 : 7-*Dimethyl*-9-(2 : 6 : 6-*trimethyl*cyclo*hex*-1-*en*-1-*yl*)*nona*-2 : 4 : 6-*trien*-8-*yn*-1-*ol* (8 : 9-*Dehydrovitamin A*) (IX).—The above ester (VIII; R = Et) (5·7 g.) in ether (40 ml.) was added dropwise to a stirred and cooled solution of lithium aluminium hydride (10 g.) in ether (36 ml.) at such a rate that the temperature did not exceed −65°. The temperature was then allowed to rise to and was kept at −30° for 1 hour. Ethyl acetate (0·8 g.) was added, the complex decomposed by addition of a saturated ammonium chloride solution (20 ml.), and the ethereal extract washed with water, dried (Na_2SO_4), and evaporated to give the crude alcohol (IX) (4·8 g.), n_D^{14} 1·6032. Light absorption (in *n*-hexane): maxima at 3280 and 2520 Å, $E_{1\,cm.}^{1\%}$ 890 and 493, respectively. This was purified either by distillation at 140°/10^{-5} mm. or by chromatography on a column of deactivated alumina (Brockmann Grade III) shielded from the light, light petroleum (b. p. 40—60°) being used as solvent, and, with the addition of 5% ether, as developer. The dehydrovitamin separated as a colourless band at the top of the column, its presence being indicated by a pale blue fluorescence in ultra-violet light. The column was cut and extracted with ether. Evaporation gave a pale yellow oil (1·2 g.), n_D^{14} 1·610. Light absorption (in *n*-hexane): maxima at 3280 and 2520 Å, $E_{1\,cm.}^{1\%}$ 1080 and 557, respectively. This oil (1·5 g.) in benzene (15 ml.) containing pyridine (5 ml.) was added to anthraquinone-2-carboxyl chloride (2·0 g.) in benzene (10 ml.), and the mixture heated on a steam-bath for 30 minutes. The material was worked up in the usual manner and the ester purified by chromatography on activated alumina, benzene–light petroleum (b. p. 40—60°) (1 : 1) being used as solvent and developer. Isolation of the chromatographed product yielded a red oil which on cooling in acetone solution gave the *anthraquinone-2-carboxylate* as fine red needles (1·1 g.), m. p. 137° (Found: C, 81·3; H, 6·8. $C_{35}H_{24}O_4$ requires C, 81·1; H, 6·5%). Light absorption (in ethanol): maxima at 3280 and 2550 Å, ε 39 400 and 66 300, respectively. If the acetone solution of the ester was subjected to rapid cooling the product was obtained in the form of small yellow needles, m. p. 113° (Found: C, 80·9; H, 6·7%). Light absorption (in ethanol): maxima at 3280 and 2550 Å, ε 39 800 and 60 600, respectively.

The above ester (0·4 g.) in 2N-alcoholic potassium hydroxide (10 ml.) was heated at 50° for 10 minutes. The product was isolated with light petroleum (b. p. 40—60°), and the crystalline residue recrystallised from *n*-pentane at −50°, to give 8 : 9-*dehydrovitamin A* as colourless needles, m. p. 47—50° (Found: C, 84·2; H, 9·8. $C_{20}H_{28}O$ requires C, 84·5; H, 9·9%). Light absorption: see Table 2.

p-*Phenylazobenzoate.* 8 : 9-Dehydrovitamin A (0·8 g.) was converted into its *p*-phenylazobenzoate by the method of Isler *et al.* (*Helv. Chim. Acta*, 1947, **30**, 1911). The crude ester was chromatographed on a column of alumina (Brockmann Grade III) in light petroleum (b. p. 40—60°)–ether (9 : 1) and crystallised from light petroleum (b. p. 40—60°) at −70°, to give the p-*phenylazobenzoate* as orange needles, m. p. 93° (Found: N, 5·7. $C_{33}H_{36}O_2N_2$ requires N, 5·7%). Light absorption (in ethanol): maxima at 3310 and 2520 Å, ε 60 800 and 24 700, respectively.

3-*Methylocta*-4 : 6-*dien*-1-*yn*-3-*ol*.—A rapid stream of acetylene was passed for 1¾ hours into liquid ammonia (6 l.), stirred and cooled in a solid carbon dioxide–alcohol bath. Calcium turnings (90 g.) were added during 1 hour, and after a further hour the acetylene flow was reduced, and crotonylideneacetone (300 g.) in dry ether (300 ml.) run in during 1 hour. The cooled mixture was stirred for another 4 hours, then ammonium chloride (470 g.) was added gradually and the ammonia evaporated on a steam-bath. Water was added to the residue and

the product was collected in ether, washed, dried, and distilled, giving a colourless oil (280 g.), b. p. 52—54°/0·8 mm., n_D^{15} 1·5075.

The oil was freed from unchanged crotonylideneacetone as described by Cheeseman, Heilbron, Jones, Sondheimer, and Weedon (*J.*, 1949, 2032), giving the desired product (200 g.), b. p. 58°/1 mm., n_D^{14} 1·5050. Light absorption (in ethanol): maximum at 2270 Å, ε 26 500.

6-*Methylocta*-3 : 5 : 7-*trien*-2-*one* (X).—A solution of 6-methylocta-3 : 5 : 7-trien-2-ol (20 g.) in light petroleum (b. p. 40—60°; 1 l.) was stirred with manganese dioxide (200 g.) for 30 minutes. The mixture was filtered and the precipitate was washed well with fresh solvent. Evaporation of the combined filtrate and washings gave a crude product (16·7 g.), n_D^{14} 1·5965. On distillation this gave a yellow oil (11·4 g.), b. p. 65°/0·4 mm., n_D^{14} 1·6025. Light absorption (in *n*-hexane): maximum at 3030 Å, ε 32 600; (in ethanol): maximum at 3110 Å, ε 31 000.

A portion of the ketone was converted into its semicarbazone and then regenerated as follows. The semicarbazone (4·5 g.) was dissolved in a mixture of glacial acetic acid (5 ml.) and pyruvic acid (50%; 5 ml.), and water was added until cloudiness appeared. The mixture was heated on a steam-bath for 15 minutes, then cooled, and treated with light petroleum (b. p. 40—60°) and much water. The light petroleum layer was dried and evaporated and the residue (2·4 g.) was distilled, giving a product (1·5 g.), b. p. 65°/0·4 mm., n_D^{16} 1·6035. Light absorption (in *n*-hexane): maximum at 3050 Å, ε 32 200.

3 : 7-*Dimethyl*-1-(2 : 6 : 6-*trimethyl*cyclo*hex*-1-*en*-1-*yl*)*nona*-4 : 6 : 8-*trien*-1-*yn*-3-*ol* (XI).—2-Ethynyl-1 : 3 : 3-trimethyl*cyclo*hex-1-ene (III) (12 g.) in ether (20 ml.) was added during 1 hour to a solution of ethylmagnesium bromide (from ethyl bromide, 13·4 g.; magnesium, 2·37 g., and ether, 30 ml.), the temperature being kept at −20°. After being stirred overnight at room temperature, the solution was cooled to −40°, and 6-methylocta-3 : 5 : 7-trien-2-one (10·4 g.) in ether (20 ml.) added during 1 hour. After a further 2 hours' stirring at −40° the complex was decomposed with ammonium chloride (30 g.) in water (120 ml.). The ethereal layer was separated, washed with water, and dried ($MgSO_4$). The solvent was evaporated *in vacuo*, finally at 10^{-5} mm. for several hours. The product (20 g., 95%) was a clear red viscous oil, n_D^{15} 1·5600. Light absorption (in *n*-hexane): maxima at 2810, 2710, and 2350 Å, $E_{1\,cm.}^{1\%}$ 950, 1100, and 625, respectively. The crude alcohol (5 g.) in light petroleum (b. p. 40—60°; 50 ml.) was chromatographed on a column of Brockmann Grade III alumina. When development with light petroleum was complete the top colourless band was cut out and eluted with ether. Distillation gave 3 : 7-*dimethyl*-1-(2 : 6 : 6-*trimethyl*cyclo*hex*-1-*en*-1-*yl*)*nona*-4 : 6 : 8-*trien*-1-*yn*-3-*ol* as a colourless viscous oil, b.p. 80—90°/10^{-5} mm., n_D^{15} 1·5630 (Found: C, 84·3; H, 9·8. $C_{20}H_{28}O$ requires C, 84·5; H, 9·85%). Active H: 1·1. Unsaturation: 5·92$\overline{|}$. Light absorption: see Table 2.

3 : 7-*Dimethyl*-9-(2 : 6 : 6-*trimethyl*cyclo*hex*-1-*en*-1-*yl*)*nona*-2 : 4 : 6-*trien*-8-*yn*-1-*ol* (IX).—A cold solution of concentrated sulphuric acid (0·4 g.) in water (80 ml.) was added to a solution of the tertiary alcohol (XI) (4 g.) in acetone (320 ml.), and the whole kept for 2 hours at room temperature in the dark; saturated sodium hydrogen carbonate solution (600 ml.) was then added, and the mixture extracted with light petroleum (b. p. 40—60°). The extracts were washed with water and dried ($MgSO_4$) and the solvent was removed *in vacuo*, to give a yellow viscous oil (4·0 g.), n_D^{15} 1·5910. Light absorption (in *n*-hexane): maxima at 3260, 2810, 2690, and 2520 Å, $E_{1\,cm.}^{1\%}$ 727, 581, 557, and 543, respectively. The crude alcohol was chromatographed on Brockmann Grade III alumina in ether–light petroleum (b. p. 40—60°) (1 : 9), the dark blue fluorescence of the purified material in ultra-violet light being used to locate it on the column. Elution with ether and evaporation of the solvent gave the alcohol (IX) (2·4 g.) as a golden-yellow viscous oil, n_D^{14} 1·6010. Light absorption (in *n*-hexane): maxima at 3280 and 2520 Å, ε 27 000 and 14 200, respectively. The identity of this material was proved by the preparation in good yield of the crystalline anthraquinone-2-carboxylate and *p*-phenylazobenzoate, whose m. p.s. were undepressed when the samples were mixed with authentic specimens (above).

Action of anhydrous methanolic hydrogen chloride on 8 : 9-*dehydrovitamin A*. (i) The alcohol (IX) (0·55 g.) was dissolved in methanolic hydrogen chloride (N/30; 50 ml.) and kept for 15 minutes. The solution was then diluted with iced water (50 ml.), neutralised with sodium hydroxide solution, and extracted with light petroleum (b. p. 40—60°), the extract dried ($MgSO_4$), and the solvent removed under reduced pressure. The residue was a pale yellow viscous liquid (0·25 g.), n_D^{14} 1·6005. Active H: 0·6. Light absorption (in *n*-hexane): maxima at 2520 and 3280 Å, $E_{1\,cm.}^{1\%}$ 508 and 1148, respectively: inflexions at 3130—3210 and 3390—3460 Å, $E_{1\,cm.}^{1\%}$ 1041 and 867, respectively.

(ii) The quantities of materials were the same as in the preceding experiment but the solution was kept for 16 hours before being worked up. The product was a pale yellow viscous oil

(0·15 g.), n_D^{16} 1·5840 (Found: C, 82·9; H, 10·2. Calc. for $C_{20}H_{28}O$: C, 84·5; H, 9·8%). Light absorption (in *n*-hexane): maxima at 2510 and 3260 Å, $E_{1\,cm.}^{1\%}$ 436 and 828, respectively: inflexion at 3360—3450 Å, $E_{1\,cm.}^{1\%}$ 649.

1-*Hex*-1′-*yn*-1′-*yl*-2 : 2 : 6-*trimethyl*cyclo*hexanol.*—Hex-1-yne (50 g.) in ether (100 ml.) was added dropwise to a stirred solution of ethylmagnesium bromide (from magnesium, 16 g.) in ether (250 ml.), and the solution heated under reflux for 2 hours. 2 : 2 : 6-Trimethyl*cyclo*hexanone (77 g.) in ether (150 ml.) was added during 30 minutes to the cooled solution (0°), which was then stirred overnight; cold saturated ammonium chloride solution (500 ml.) was added, the product extracted with ether, and the ethereal extract washed with sodium hydrogen carbonate, dried (Na_2SO_4), and evaporated. Distillation of the product through a 12″ Fenske column gave 1-*hex*-1′-*yn*-1′-*yl*-2 : 2 : 6-*trimethyl*cyclo*hexanol* as a colourless liquid (62 g.), b. p. 133—140°/12 mm., n_D^{15} 1·4800 (Found: C, 81·0; H, 11·6. $C_{15}H_{26}O$ requires C, 81·0; H, 11·8%). Active H: 1·15. Unsaturation: 2·0|=.

Dehydration of 1-*hex*-1′-*yn*-1′-*yl*-2 : 2 : 6-*trimethyl*cyclo*hexanol.*

(2 G. of alcohol were used in all these experiments.)

Dehydrating agent	Conditions of reaction	Product: Wt., g.	Product: n_D^{14}	Product: $\lambda_{max.}$, Å	Product: $E_{1\,cm.}^{1\%}$
Ac_2O containing 1% H_2SO_4 (7 ml.)	0°, 20 min.	0·6	1·4927 *	2320	607
H_2SO_4 (50%; 10 ml.)	50°, 4 hours	1·3	1·4860 *	2330	288
Toluene-*p*-sulphonic acid (1·0 g.)	Refluxed in PhMe (300 ml.) until no further water evolved	1·0	1·4940	2410	180
Iodine (0·1 g.)	As above	1·0	1·4900	2330	181
$H{\cdot}CO_2H$ (98%; 10 ml.)	Reflux for 10 min.	1·1	1·4798	2270	121
$POCl_3$ (1·0 g.)	Heated in pyridine (8·0 ml.) at 50° for 2 hours	1·1	1·4799	2280	38
Ac_2O (10 ml.)	Reflux for 2 hours	1·2	1·4947	2320	512

* n_D^{15}.

Prepared by the first method and isolated in the usual way, 1-*hex*-1′-*yn*-1′-*yl*-2 : 6 : 6-*trimethyl*cyclo*hex*-1-*ene* was obtained after fractionation twice through a short column; b.p. 130°/13 mm., n_D^{14} 1·4940 (Found: C, 88·3; H, 12·1. $C_{15}H_{24}$ requires C, 88·2; H, 11·8%). Unsaturation: 2·95 |=. Light absorption (in ethanol): maximum at 2300 Å, ϵ 12 540.

1-(1-*Hydroxy*-2 : 2 : 6-*trimethyl*cyclo*hexyl*)-3-*methylocta*-4 : 6-*dien*-1-*yn*-3-*ol* (XII).—1-Ethynyl-2 : 2 : 6-trimethyl*cyclo*hexanol (20 g.) in ether (50 ml.) was added dropwise to a refluxing solution of ethylmagnesium bromide (from magnesium, 7·2 g.) in ether (400 ml.), and the mixture stirred for a total of 2 hours. It was cooled to 20° and freshly distilled crotonylideneacetone (19·8 g.) in ether (50 ml.) was added. After being stirred for a further 2 hours, it was cooled to 0°, and aqueous ammonium chloride (20% solution; 500 ml.) added at such a rate that the temperature did not exceed 20°. The product was extracted with ether, the ethereal extract evaporated under reduced pressure, and the residue distilled, giving the *diol* (XII) as a pale yellow viscous oil (20·3 g.), b. p. 120°/10^{-5} mm.; n_D^{15} 1·5240 (Found: C, 78·3; H, 10·5. $C_{18}H_{28}O_2$ requires C, 78·2; H, 10·2%). Active H: 2·1. Unsaturation 3·8|=. Light absorption: see Table 2.

8-(1-*Hydroxy*-2 : 2 : 6-*trimethyl*cyclo*hexyl*)-6-*methylocta*-3 : 5-*dien*-7-*yn*-2-*ol* (XIV).—(i) The foregoing glycol (XII) (5·25 g.) in ether (20 ml.) was shaken for 16 hours with dilute hydrochloric acid (0·5%; 20 ml.). The aqueous layer was re-extracted with ether, and the combined ethereal solutions washed with saturated sodium hydrogen carbonate solution, dried (Na_2SO_4), and evaporated. Distillation gave the *glycol* (XIV) as a very viscous yellow gum (3·3 g.), b. p. 120°/10^{-4} mm., n_D^{14} 1·5445 (Found: C, 78·0; H, 10·2. $C_{18}H_{28}O_2$ requires C, 78·2; H, 10·2%). Active H: 2·0. Unsaturation: 3·8|=. Light absorption: see Table 2.

(ii) The glycol (XII) (8·9 g.) in acetone (250 ml.) was added to an aqueous solution of hydrochloric acid (1%; 100 ml.) and kept for 4 hours. The solution was neutralised by addition of saturated sodium hydrogen carbonate solution (350 ml.), and the product isolated with light petroleum (b. p. 40—60°). Distillation gave the rearranged glycol (XIV) (7·2 g.), b. p. 130°/10^{-5} mm., n_D^{18} 1·5431.

(iii) 6-Methylocta-3 : 5-dien-7-yn-2-ol (XIII) (13·6 g.) in ether (50 ml.) was added dropwise to a stirred solution of ethylmagnesium bromide (from magnesium, 5·34 g.) in ether (200 ml.). The mixture was heated under reflux for 30 minutes, cooled to room temperature, and 2 : 2 : 6-trimethyl*cyclo*hexanone (14 g.) in ether (50 ml.) added during 2 hours. The mixture was again heated under reflux for 30 minutes and cooled to 20°. Saturated ammonium chloride solution (100 ml.) was added, and the product isolated with ether. Distillation gave the glycol (XIV)

(12·6 g.) as a viscous yellow gum, b. p. 120°/10^{-5} mm., n_D^{14} 1·5447. Light absorption (in *n*-hexane): maxima at 2690 and 2810 Å, ε 30 400 and 23 000, respectively.

6-*Methylocta*-3:5-*dien*-7-*yn*-2-*one*.—6-Methylocta-3:5-dien-7-yn-2-ol (4·0 g.), dissolved in light petroleum (b. p. 40—60°; 200 ml.), was shaken with manganese dioxide (40 g.) for 45 minutes. The dioxide was removed by filtration, and the filtrate split into two equal portions which were treated as follows: (*a*) The solvent was removed under reduced pressure, the temperature of the solution being kept below 5°, leaving 6-*methylocta*-3:5-*dien*-7-*yn*-2-*one* (1·3 g.) as a pale red liquid, n_D^{14} 1·5665 (Found: C, 80·4; H, 7·5. $C_9H_{10}O$ requires C, 80·3; H, 7·5%). Light absorption (in *n*-hexane): maximum at 3030 Å, ε 18 300; inflection at 2630—2710 Å, ε 12 000. (*b*) After removal of the solvent the residue (1·5 g.) was converted in the usual manner into the *semicarbazone*, pale yellow plates (from ethanol), m. p. 120° (decomp.) (Found: C, 62·7; H, 6·8; N, 20·4. $C_{10}H_{13}ON_3$ requires C, 62·8; H, 6·9; N, 22·0%). Light absorption (in ethanol): maxima at 3270 and 3130 Å, ε 47 700 and 50 000, respectively.

8-(1-*Hydroxy*-2:2:6-*trimethyl*cyclo*hexyl*)-6-*methylocta*-3:5-*dien*-7-*yn*-2-*one* (XV).—(i) The C_{18} glycol (XIV) (20 g.), aluminium *tert.*-butoxide (45 g.) in dry acetone (1 l.), and dry benzene (750 ml.) were heated under reflux for 40 hours. The cooled mixture was decomposed with 2N-sulphuric acid (2 l.), and the benzene layer washed with sodium hydrogen carbonate solution, dried ($MgSO_4$), and evaporated. Distillation gave a viscous yellow liquid (15 g.), b. p. 135°/10^{-5} mm., n_D^{14} 1·5595. Light absorption (in *n*-hexane): maxima at 3020 and 2240 Å, $E_{1\,cm.}^{1\%}$ 742 and 450, respectively.

(ii) The glycol (XIV) (30 g.) in carbon tetrachloride (900 ml.) was stirred with manganese dioxide (300 g.) for 1 hour. After filtration, the filtrate was evaporated and the residue distilled to give a viscous oil (20 g.), n_D^{14} 1·5678. Light absorption (in *n*-hexane): maximum at 3000 Å, $E_{1\,cm.}^{1\%}$ 946. Inflection at 3030—3130 Å, $E_{1\,cm.}^{1\%}$ 831.

The *semicarbazone*, prepared in the usual manner, formed fine needles (from aqueous methanol), m. p. 194° (sintered, 140—145°) (Found: N, 12·6. $C_{19}H_{29}O_2N_3$ requires N, 12·7%). Light absorption (in ethanol): maxima at 3330, 3160, and 2320 Å, ε 43 500, 49 800, and 4300, respectively.

The semicarbazone (8·5 g.), 2N-sulphuric acid (100 ml.), and light petroleum (b. p. 80—100°; 200 ml.) were heated under reflux with rapid stirring for 6 hours. The organic layer was separated, washed with sodium hydrogen carbonate solution, dried (Na_2SO_4), and evaporated. Distillation gave 8-(1-*hydroxy*-2:2:6-*trimethyl*cyclo*hexyl*)-6-*methylocta*-3:5-*dien*-7-*yn*-2-*one* as a viscous yellow liquid (4·2 g.), b. p. 140°/10^{-4} mm., n_D^{18} 1·5708 (Found: C, 78·8; H, 9·6. $C_{18}H_{26}O_2$ requires C, 78·6; H, 9·6%). Active H: 1·05. Unsaturation: 3·9|=. Light absorption: see Table 2.

6-*Methyl*-8-(2:6:6-*trimethyl*cyclo*hex*-1-*en*-1-*yl*)*octa*-3:5-*dien*-7-*yn*-2-*one* (VI).—A mixture of the hydroxy-ketone (XV) (50 g.) and toluene-*p*-sulphonic acid (2 g.) in toluene (2 l.) was distilled slowly until the distillate was free from traces of water (2½ hours). The residue was washed with saturated sodium hydrogen carbonate solution, dried (Na_2SO_4), and evaporated. Distillation gave the dehydro-C_{18} ketone (VI) (34 g.) as a pale yellow liquid, b. p. 140°/10^{-5} mm., n_D^{15} 1·5960. Light absorption (in *n*-hexane): maxima at 3380 and 2440 Å, $E_{1\,cm.}^{1\%}$ 741 and 447, respectively. The semicarbazone was prepared and had m. p. 204—205° undepressed when the sample was mixed with an authentic specimen (above).

Ethyl 3-*Hydroxy*-9-(1-*hydroxy*-2:2:6-*trimethyl*cyclo*hexyl*)-3:7-*dimethylnona*-4:6-*dien*-8-*yne*-1-*carboxylate* (XVI).—The hydroxy-ketone (XV) (5·5 g.), ethyl bromoacetate (8·0 g.), activated zinc (3·0 g.), and a crystal of iodine in benzene (50 ml.) were heated under reflux for 2 hours. The product gave the *ethyl* ester (XVI) as a viscous red liquid (5·7 g.), n_D^{14} 1·5318 (Found: C, 72·8; H, 9·1; OEt, 11·1. $C_{20}H_{32}O_3$·OEt requires C, 72·9; H, 9·5; OEt, 12·4%). Active H: 2·2. Light absorption: see Table 2.

Ethyl 9-(1-*Hydroxy*-2:2:6-*trimethyl*cyclo*hexyl*)-3:7-*dimethylnona*-2:4:6-*trien*-8-*yne*-1 *carboxylate* (XVII).—The foregoing ester (XVI) (2·0 g.) and toluene-*p*-sulphonic acid (0·05 g.) in benzene (150 ml.) were heated under reflux for 5 hours. Isolation of the product in the usual manner gave a dark viscous oil (0·9 g.), n_D^{14} 1·6000, which was chromatographed on a column of deactivated alumina with light petroleum (b. p. 40—60°) as solvent and developer, and gave the *ethyl* ester (XVII) as a pale yellow viscous liquid, n_D^{14} 1·605—1·610 (Found: C, 77·0; H, 8·8; OEt, 11·4. $C_{20}H_{27}O_2$·OEt requires C, 76·7; H, 9·4; OEt, 13·1%). Active H: 0·85. Light absorption: see Table 2.

Ethyl 3:7-*Dimethyl*-9-(2:6:6-*trimethyl*cyclo*hex*-1-*en*-1-*yl*)*nona*-2:4:6-*trien*-8-*yne*-1-*carboxylate* (VIII; R = Et).—The glycol ester (XVI) (2·9 g.), toluene-*p*-sulphonic acid (0·85 g.), and toluene (150 ml.) were heated under reflux for 5 hours. Isolation of the crude product and

purification by chromatography on a column of deactivated alumina by use of light petroleum (b. p. 40—60°) as solvent and developer gave 8 : 9-dehydrovitamin A acid ethyl ester (VIII; R = Et) (0·7 g.), n_D^{14} 1·620—1·623 (Found : C, 80·9 ; H, 9·2 ; OEt, 13·6. Calc. for $C_{20}H_{25}O_2$·OEt : C, 80·9 ; H, 9·3 ; OEt, 13·8%).

1-(1-*Hydroxy*-2 : 2 : 6-*trimethyl*cyclo*hexyl*)-3 : 7-*dimethylnona*-4 : 6 : 8-*trien*-1-*yn*-3-*ol* (XVIII). —A solution of 1-ethynyl-2 : 2 : 6-trimethyl*cyclo*hexanol (16·6 g.) in benzene (150 ml.) was added to a solution of ethylmagnesium bromide (from magnesium, 5·84 g.) in ether (50 ml.), the mixture stirred under reflux for 30 minutes and then cooled to room temperature, and 6-methylocta-3 : 5 : 7-trien-2-one (13·6 g.) in benzene (150 ml.) was added in about 30 minutes. The solution was refluxed for 15 minutes, cooled, and poured on ice and ammonium chloride solution. The benzene layer was washed, dried, and evaporated *in vacuo*, leaving an oil (31·1 g.). Light absorption (in ethanol) : maximum at 2690 Å, $E_{1\text{ cm.}}^{1\%}$ 1180. A sample of this material was purified for analysis by chromatography on alumina (Brockmann Grade I), followed by distillation, giving the *diol* (XVIII) as a yellow oil, b. p. 160—180°/10^{-5} mm., n_D^{15} 1·5493 (Found : C, 79·4 ; H, 10·2. $C_{20}H_{30}O_2$ requires C, 79·4 ; H, 10·0%). Light absorption : see Table 2.

9-(1-*Hydroxy*-2 : 2 : 6-*trimethyl*cyclo*hexyl*)-3 : 7-*dimethylnona*-2 : 4 : 6-*trien*-8-*yn*-1-*ol* (XIX). —The preceding product (XVIII) (16·5 g.) was dissolved in aqueous acetone (90% ; 330 ml.) containing sulphuric acid (0·1% w/v), and the solution, after 3 hours at room temperature, was poured into a large volume of water. The product was collected in ether (sodium sulphate being used to break emulsions), the solution washed with alkali and water, and the solvent evaporated. The residual viscous oil (15·9 g.) was taken up in *cyclo*hexane (50 ml.), and, on cooling and seeding, the solution deposited the *diol* (XIX) as colourless hexagonal plates (4·3 g.), m. p. 76—80°, raised by recrystallisation from the same solvent to 78—80° (Found : C, 79·3 ; H, 10·1. $C_{20}H_{30}O_2$,$\frac{1}{4}C_6H_{12}$ requires C, 79·8 ; H, 10·3%). Active H : 2·05. Light absorption (in ethanol) : maxima at 3170, 3020, and 2260 Å, ε 36 500, 45 300, and 7730, respectively ; inflection at 2870—2960 Å, ε 34 400. The compound gave a green colour with the Carr–Price reagent.

When the crystals were heated at 56°/0·1 mm. they lost 6·5% of their weight (corresponding to ¼ mol. of *cyclo*hexane of crystallisation) and then had m. p. 93—95° (Found : C, 79·2 ; H, 10·1. $C_{20}H_{30}O_2$ requires C, 79·4 ; H, 10·0%). Light absorption : see Table 2. The same unsolvated *compound* was also obtained by recrystallisation of the *cyclo*hexane-containing crystals from ether. The higher-melting solid reverted to the original solvated modification on recrystallisation from *cyclo*hexane.

The necessary seed crystals were obtained *via* the *anthraquinone-2-carboxylate* as follows. Dry pyridine (6 ml.) was added to a solution of the crude glycol (6 g.) and anthraquinone-2-carboxyl chloride (3·2 g.) in dry benzene (50 ml.) and the mixture was refluxed for 45 minutes. Water (6 ml.) was added to the mixture which was then shaken for a few minutes and filtered. The filtrate was washed successively with dilute hydrochloric acid, sodium hydroxide solution and water, dried, and evaporated. The residue, after trituration with ether, afforded a solid product (1·3 g.), m. p. 180—182°, which separated from benzene in pale yellow prisms, m. p. 181—182°, resolidifying sharply at 183°, and again melting gradually with decomposition up to about 220° (Found : C, 78·3 ; H, 6·7. $C_{35}H_{34}O_5$ requires C, 78·3 ; H, 6·7%). Light absorption (in chloroform) : maxima at 2580, 2800, 3060, and 3200 Å, ε 62 500, 31 400, 41 600, and 38 000, respectively.

The anthraquinone-2-carboxylate (0·2 g.) was hydrolysed by heating it with 2N-alcoholic potassium hydroxide (5 ml.) at 50° for 10 minutes. The mixture was then filtered, and the filtrate poured into water. The product was collected by means of ether and recrystallised twice from *cyclo*hexane, to give material, m. p. 78—80°, identical with that described above.

4-(1-*Hydroxy*-2 : 6 : 6-*trimethyl*cyclo*hexyl*)*but*-3-*yn*-2-*ol*.—1-Ethynyl-2 : 2 : 6-trimethyl*cyclo*hexanol (14·3 g.) in ether (50 ml.) was added to a stirred refluxing solution of ethylmagnesium bromide (magnesium, 5 g. ; ethyl bromide, 28 g. ; ether, 70 ml.), and the product refluxed for 2 hours. It was cooled to −10°, and freshly distilled acetaldehyde (3·8 g.) in ether (25 ml.) added with stirring. Stirring was continued for 2 hours while the mixture warmed to 5°. On isolation of the product in the usual way, followed by distillation at 0·15 mm. through a short column, the *diol* (13·1 g., 72·5%) was obtained, b. p. 107—108°/0·15 mm. It solidified and gave prisms, m. p. 112—113°, from light petroleum (b. p. 100—120°) (Found : C, 74·1 ; H, 10·35. $C_{13}H_{22}O_2$ requires C, 74·25 ; H, 10·55%). Active H : 2·1.

The standard procedure gave the 3 : 5-*dinitrobenzoate* as pale yellow needles, m. p. 132·5—133·5°, from ethanol (Found : C, 59·2 ; H, 6·0 ; N, 7·15. $C_{20}H_{24}O_7N_2$ requires C, 59·4 ; H, 6·0 ; N, 6·95%).

4-(1-*Hydroxy*-2 : 2 : 6-*trimethyl*cyclo*hexyl*)*but*-3-*yn*-2-*one*.—(i) The foregoing diol (1 g.) in light

petroleum (b. p. 40—60°; 50 ml.) was stirred with active manganese dioxide (10 g.) for 1 hour. The product was distilled and gave the *hydroxy-ketone* (0·65 g.), b. p. 100°/0·1 mm., n_D^{14} 1·4994 (Found: C, 74·7; H, 9·5. $C_{13}H_{20}O_2$ requires C, 74·95; H, 9·7%). Active H: 0·8. Light absorption (in *n*-hexane): maxima at 2190 and 2980 Å, ε 7500 and 97, respectively. (ii) 1-Ethynyl-2 : 2 : 6-trimethyl*cyclo*hexanol (10·6 g.) in ether (30 ml.) was treated with a solution of ethylmagnesium bromide (magnesium, 3·7 g.; ethyl bromide, 20 g.; ether, 50 ml.) as above, and after 2 hours' refluxing the solution was cooled to room temperature. It was added to a stirred solution of acetic anhydride (6·6 g.) in ether (50 ml.) at −65°, and the product stirred for 2 hours while it warmed to 10°. On isolation in the normal way and distillation at 0·1 mm., a fraction, b. p. 100—105° (6·06 g.; 45%), was collected and redistilled. It had b. p. 90°/0·05 mm., n_D^{14} 1·4957. Light absorption (in *n*-hexane): maxima at 2200 and 2950 Å, $E_{1\,cm.}^{1\%}$ 340 and 4·35, respectively.

8-(1-*Hydroxy*-2 : 2 : 6-*trimethyl*cyclo*hexyl*)-6-*methylocta*-3 : 5 : 7-*trien*-2-*ol* (XX).—A solution of the C_{18} acetylenic glycol (XIV) (20·2 g.) in ether (500 ml.) was added to a stirred solution of lithium aluminium hydride (3·5 g.) in ether (167 ml.) during 20 minutes. The mixture was stirred under reflux for 3 hours, then cooled at 0° and treated cautiously with ice, followed by a solution of tartaric acid (10 g.) in water (500 ml.). The ethereal layer was washed, dried, and evaporated *in vacuo*, leaving an oil (19 g.). Light absorption (in *n*-hexane): maxima at 2410, 2750, and 3130 Å, $E_{1\,cm.}^{1\%}$ 550, 615, and 295, respectively. This oil was dissolved in light petroleum (b. p. 40—60°; 50 ml.) and chromatographed on Brockmann Grade III alumina (400 g.). The chromatogram was developed with light petroleum until the two yellow bands which fluoresced in ultra-violet light had reached the middle of the column. The portion of the column above these bands was eluted with ether and gave, on evaporation, a yellow oil (10·5 g.), which was used for the next stage. Light absorption (in *n*-hexane): maxima at 2740 and 3130 Å, $E_{1\,cm.}^{1\%}$ 911 and 235, respectively. Infra-red absorption analysis showed 91% reduction of the triple bond. Further purification of this material by chromatography gave 8-(1-*hydroxy*-2 : 2 : 6-*trimethyl*-cyclo*hexyl*)-6-*methylocta*-3 : 5 : 7-*trien*-2-*ol* as a colourless viscous oil, n_D^{15} 1·5530 (Found: C, 77·9; H, 10·8. $C_{18}H_{30}O_2$ requires C, 77·7; H, 10·8%). Active H: 2·0. Unsaturation: 3·15$\overline{\Box}$. Light absorption: see Table 2.

8-(1-*Hydroxy*-2 : 2 : 6-*trimethyl*cyclo*hexyl*)-6-*methylocta*-3 : 5 : 7-*trien*-2-*one* (XXI).—A solution of the triene glycol (XX) (7 g.) in light petroleum (b. p. 40—60°; 350 ml.) was stirred with manganese dioxide (70 g.) for 30 minutes. The mixture was filtered, and the solid washed with light petroleum (350 ml.) The filtrate was evaporated *in vacuo*, leaving a yellow oil (6·1 g.), n_D^{17} 1·5720, which was used for the next stage. Light absorption (in *n*-hexane): maxima at 2250 and 3130 Å, $E_{1\,cm.}^{1\%}$ 340 and 925, respectively. A sample of this *hydroxy-ketone* was purified by chromatography in light petroleum (b. p. 40—60°) on Brockmann Grade II alumina, followed by distillation, and was obtained as a viscous yellow oil, b. p. 130°/10^{-4} mm., n_D^{15} 1·5773 (Found: C, 78·2; H, 10·4. $C_{18}H_{28}O_2$ requires C, 78·2; H, 10·2%). Active H: 1·15. Unsaturation: 2·9$\overline{\Box}$. Light absorption: see Table 2. The *semicarbazone* separated from methanol as yellow microcrystalline powder, m. p. 213—215° (Found: C, 68·5; H, 9·4; N, 12·6. $C_{19}H_{31}O_2N_3$ requires C, 68·5; H, 9·3; N, 12·6%). Light absorption (in ethanol): maxima at 2350, 3250, and 3400 Å, ε 4900, 57 500, and 48 600, respectively.

The semicarbazone (1·0 g.) was refluxed with light petroleum (b. p. 100—120°; 10 ml.) and 2N-hydrochloric acid (20 ml.) for 2 hours. A yellow oil (0·4 g.), n_D^{15} 1·6024, was isolated from the petroleum layer. Light absorption (in *n*-hexane): maxima at 2250 and 3240 Å, $E_{1\,cm.}^{1\%}$ 253 and 1088, respectively.

6-*Methyl*-8-(2 : 6 : 6-*trimethyl*cyclo*hex*-1-*en*-1-*yl*)*octa*-3 : 5 : 7-*trien*-2-*one*.—A solution of the hydroxy-ketone (XXI) (9·2 g.) and toluene-*p*-sulphonic acid (0·18 g.) in dry toluene (230 ml.) was refluxed for 30 minutes. The solution was washed with aqueous sodium hydrogen carbonate and water, and the solvent removed *in vacuo*. The residue was partly purified by chromatography on Brockmann Grade II alumina in light petroleum (b. p. 40—60°). The chromatogram was developed until the area which appeared brown in ultra-violet light had reached the bottom of the column. Extraction of the column with ether, evaporation of the solvent, and distillation of the residue gave a pale yellow viscous oil (1·9 g.), b.p. 120°/10^{-4} mm., n_D^{16} 1·5900. Light absorption (in *n*-hexane): maximum at 3280 Å, $E_{1\,cm.}^{1\%}$ 755. The semicarbazone separated from methanol as yellow plates, m. p. 190—192° (decomp.) undepressed when the sample was mixed with an authentic specimen prepared from β-ionone by the method of van Dorp and Arens (*Rev. Trav. chim.*, 1946, **65**, 338) (Found: C, 72·3; H, 9·4; N, 13·2. Calc. for $C_{15}H_{29}ON_3$: C, 72·4; H, 9·2; N, 13·3%). Light absorption (in ethanol): maximum at 3450 Å, ε 53 900.

The semicarbazone (0·54 g.) was refluxed with light petroleum (b. p. 100—120°; 15 ml.)

and 2N-hydrochloric acid (15 ml.) for 2 hours. A viscous yellow oil, b. p. 120°/10^{-4} mm, n_D^{17} 1·6230, was isolated from the petroleum layer (Found: C, 83·7; H, 10·2. Calc. for $C_{18}H_{26}O$: C, 83·9; H, 10·1%). Unsaturation: 3·8|=. Light absorption: see Table 2.

9-(1-*Hydroxy*-2 : 2 : 6-*trimethyl*cyclo*hexyl*)-3 : 7-*dimethylnona*-2 : 4 : 6 : 8-*tetraen*-1-*ol* (XXII; R = H).—A solution of 9-(1-hydroxy-2 : 2 : 6-trimethyl*cyclo*hexyl)-3 : 7-dimethylnona-2 : 4 : 6-trien-8-yn-1-ol (XIX) (3 g.) in ether (150 ml.) was added to a stirred solution of lithium aluminium hydride (0·75 g.) in dry ether (190 ml.) during 1 hour. The mixture was stirred under reflux for 3 hours, then cooled to 0° and treated cautiously with ice and a saturated solution of tartaric acid. The ethereal layer was washed with saturated tartaric acid solution and water, dried, and evaporated *in vacuo*, leaving a pale yellow oil (2·8 g.). Crystallisation from *cyclo*hexane gave the *diol* (XXII; R = H) as needles, m. p. 122—127° (Found: C, 78·7; H, 10·6. $C_{20}H_{32}O_2$ requires C, 78·95; H, 10·5%). Active H: 1·8. Unsaturation: 3·6|=. Light absorption: see Table 2.

9-(1-*Hydroxy*-2 : 2 : 6-*trimethyl*cyclo*hexyl*)-3 : 7-*dimethylnona*-2 : 4 : 6 : 8-*tetraen*-1-*yl Acetate* (XXII; R = Ac).—A solution of acetyl chloride (1·75 g.) in dry ether (70 ml.) was added during 30 minutes to a solution of the above glycol (XXII; R = H) (3·4 g.) and dry pyridine (5·4 ml.) in dry ether (70 ml.) cooled to 0°, so that the temperature did not exceed 10°. The mixture was kept at room temperature for 40 minutes, and decomposed with N-sulphuric acid with cooling, so that the temperature did not exceed 10°. The ethereal layer was washed with N-sulphuric acid and saturated sodium hydrogen carbonate solution, dried, and evaporated *in vacuo*, leaving a crystalline residue (3·6 g.; m. p. 96—104°). Recrystallisation from *cyclo*hexane gave the *acetate* (XXII; R = Ac), m. p. 110—111° (Found: C, 75·9; H, 9·75. $C_{22}H_{34}O_3$ requires C, 76·3; H, 9·8%). Active H: 1·15. Unsaturation: 3·95|=.

Vitamin A Acetate.—A solution of the hydroxy-acetate (XII; R = Ac) (3 g.) and toluene-*p*-sulphonic acid (18 mg.) in toluene (450 ml.) was heated at 80° for 30 minutes. The cooled solution was washed with saturated sodium hydrogen carbonate solution and water, dried, and evaporated *in vacuo*. The residue [light absorption (in ethanol): maxima at 3270, 3680, and 3900 Å, $E_{1\,cm.}^{1\%}$ 741, 514, and 321, respectively. Inflexion at 3390—3490 Å, $E_{1\,cm.}^{1\%}$ 641] was chromatographed on Brockmann Grade III alumina in a 1 : 1 mixture of light petroleum (b. p. 40—60°) and benzene. Development was continued until the required fraction, which had a bright blue fluorescence in ultra-violet light, had been washed through. Evaporation *in vacuo* gave impure vitamin A acetate (1·66 g.). Light absorption (in ethanol): maxima at 3300, 3680, and 3910 Å, $E_{1\,cm.}^{1\%}$ 892, 767, and 503, respectively.

Vitamin A Anthraquinone-2-carboxylate.—The above impure vitamin A acetate (1·66 g.) was warmed with methanol (5 ml.) and N-methanolic potassium hydroxide (14 ml.) to 50° for 10 minutes. The product was poured into iced water, extracted with light petroleum (b. p. 40—60°), and washed with water until neutral. The dried solution was evaporated *in vacuo*, leaving a residue (1·5 g.) which was dissolved in benzene (15 ml.) and dry pyridine (5 ml.). This solution was treated with anthraquinone-2-carboxyl chloride (1·95 g.) in benzene (15 ml.) and heated on a steam-bath for 35 minutes. A dark red oil (1·55 g.) was isolated in the usual way. This was chromatographed on Brockmann Grade III alumina in a 1 : 1 mixture of light petroleum (b. p. 40—60°) and benzene. A chocolate-brown band, which moved slowly down the column, was extracted with ether to yield a fraction (0·6 g.). Light absorption (in alcohol): maxima at 2560 and 3280 Å, $E_{1\,cm.}^{1\%}$ 858 and 737, respectively. This fraction crystallised from acetone and gave vitamin A anthraquinone-2-carboxylate as pale yellow prisms, m. p. 124°, undepressed when the sample was mixed with a specimen prepared from natural vitamin A. Light absorption in (ethanol): maxima at 2550 and 3290 Å, $E_{1\,cm.}^{1\%}$ 983 and 1010, respectively. The red modification, m. p. 117—119°, was also obtained.

We acknowledge our indebtedness to Sir Ian Heilbron, F.R.S., and Professor E. R. H. Jones, F.R.S., for first bringing to our notice the possibility of a synthesis on these lines, and for their continued interest and advice. We also thank Dr. A. W. Taylor, of Imperial Chemical Industries Limited, Billingham, and Dr. E. A. Coulson, of the Chemical Research Laboratory, Teddington, for the infra-red spectra, Miss R. Russell for the ultra-violet spectra, and Miss H. King for the microanalyses.

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195. *Substituted Anthracene Derivatives. Part V.* The Conjugating Powers of the Substitution Positions in* 1 : 2-*Benzanthracene.*

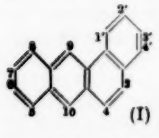
By G. M. Badger, R. S. Pearce, and R. Pettit.

The ultra-violet absorption spectra of several monomethyl-1 : 2-benzanthracenes are very similar to that of the parent hydrocarbon except that the bands are shifted to somewhat longer wave-lengths. The bathochromic shifts produced by methyl substitution in each of the twelve possible positions have been compared with the conjugating powers of these positions calculated by the method of molecular orbitals.

One of the most interesting problems in aromatic chemistry still awaiting adequate experimental investigation concerns the relative conjugating powers of the various positions in an aromatic ring system. In the case of naphthalene, evidence is accumulating that the conjugating power of the 1- is much greater than that of the 2-position. For example, Ketelaar and Oosterhout (*Rec. Trav. chim.*, 1946, **65**, 448) have examined the dipole moments of the halogenated naphthalenes and have concluded that the C–Cl bond in 1-chloronaphthalene has about 14·2% double-bond character as against 13·0% for 2-chloronaphthalene. Similarly, Badger (*Nature*, 1950, **165**, 647; see also Coulson, *J.*, 1950, 2252) has examined the rates of oxidation of the dinaphthylethylenes with osmium tetroxide, and has shown that an ethylenic double bond is conjugated to the 1- to a much greater extent than to the 2-position. For the azonaphthalenes, the rates of oxidation with perbenzoic acid indicate that an azo-group is conjugated to the 1- to a greater degree than to the 2-position (Badger and Lewis, *Nature*, 1951, **167**, 403). Furthermore, the basic strengths of 1- and 2-naphthylamines also confirm the superior conjugating ability of the 1-position. Very few data are available for other aromatic hydrocarbons, however, and it therefore seemed of interest to attempt to estimate the conjugating powers of the various substitution positions in 1 : 2-benzanthracene by a spectroscopic method.

Substituents in benzenoid aromatic compounds have long been known to produce shifts in the positions of the absorption bands to longer wave-lengths (bathochromic shifts), and it seems to be established that the magnitude of the shift produced depends on the extent of electronic interaction between the substituent and the ring (cf. Doub and Vandenbelt, *J. Amer. Chem. Soc.*, 1947, **69**, 2714; Badger and Pearce, *J.*, 1950, 3072). Indeed, the magnitude of the bathochromic shift can be used to determine the relative degrees of conjugation of different substituents with the benzene ring (cf. Kiss, Molnár and Sandorfy, *Compt. rend.*, 1948, **227**, 724). It is therefore reasonable to suppose that the magnitude of the bathochromic shifts produced by a given substituent at the various possible positions of substitution should give a measure of the relative conjugating powers of the different positions.

1 : 2-Benzanthracene (I) seemed to be a suitable compound for examination as its spectrum shows a number of sharp bands, and as there are twelve possible positions of substitution. All twelve monomethyl derivatives have been described (Cook and Robinson, *J.*, 1938, 505), and the absorption spectra of six of these have already been reported in detail by Jones (*J. Amer. Chem. Soc.*, 1940, **62**, 148). Through the courtesy of Professor M. S. Newman, who has recently devised new and more satisfactory syntheses (Newman and Gaertner, *ibid.*, 1950, **72**, 264) and who has kindly presented us with samples of the remaining isomers, it has now been possible to complete the series.


(I)

The absorption bands in the spectrum of 1 : 2-benzanthracene (Fig. 1) have been labelled *A*—*K* in agreement with Jones and with previous work from this laboratory. These bands fall into three main groups: I, bands *ABCDE*; II, bands *FGHI*; III, bands *I′JK*. Most of the monomethyl derivatives show similar spectra except that the bands are shifted somewhat to longer wave-lengths. The data for six of the monomethylbenzanthracenes have been tabulated by Jones (*loc. cit.*); and the positions of the absorption peaks, together

* Part IV, *J.*, 1950, 3072.

with the extinction coefficients of the remaining six isomers which have now been examined, are collected in Table 1. The spectra of some of the isomers show a certain loss of fine structure and this sometimes makes it difficult to identify all the bands with certainty. In every case, however, the *D* band is quite clear and distinct; and there is also little danger of wrong identification with the *H* band. The approximately constant frequency difference between the bands in each of the main three groups also assists identification (cf. Badger and Pearce, *loc. cit.*).

TABLE 1. *Positions of the maxima and corresponding intensities* (log $E_{max.}$) *in the ultra-violet absorption spectra of* 1 : 2-*benzanthracene and of the methyl*-1 : 2-*benzanthracenes* (*solvent, ethanol*).*

Position of methyl substituent	*A*	*B*	*C*	*D*	*E*	*F*	*G*	*G'*	*H*	*H'*	*I*	*I'*	*J*	*K*
†	2560	2670	2770	2875	2995	3140	3265	—	3410	—	3585	(3635)	3755	3845
	4·56	4·62	4·90	4·99	3·95	3·67	3·81	—	3·87	—	3·72	3·46	2·73	2·95
2'-	2585	2690	2800	2910	3015	—	3270	3330	3425	3485	3590	3660	3765	3880
	4·57	4·63	4·87	4·92	3·93	—	3·79	3·80	3·87	3·77	3·74	3·46	2·79	3·16
3'-	2580	2685	2780	2890	3015	3150	3290	—	3435	—	3605	—	3760	3855
	4·45	4·55	4·81	4·89	4·03	3·75	3·83	—	3·84	—	3·64	—	2·66	2·69
4'-	2550	2720	2820	2930	3025	3160	3290	—	3445	—	3620	—	3780	3880
	4·57	4·63	4·89	4·95	4·09	3·73	3·87	—	3·93	—	3·78	—	2·73	3·03
3-	2570	2705	2800	2910	2995	3115	3260	3345	3405	3500	3570	3670	3770	3880
	4·63	4·68	4·90	4·96	4·22	3·71	3·82	3·79	3·86	3·70	3·71	3·27	2·76	3·12
6-	2570	2695	2790	2890	3010	3145	3300	—	3435	—	3600	—	(3770)	3850
	4·58	4·61	4·85	4·92	4·16	3·72	3·83	—	3·81	—	3·60	—	2·61	2·48
7-	2575	2680	2780	2885	3015	—	3255	3330	3405	3490	3570	3670	3770	3875
	4·63	4·66	4·90	5·01	4·04	—	3·80	3·80	3·84	3·74	3·67	3·39	2·78	3·18

* Figures in parentheses are points of inflexion. † Parent compound.

TABLE 2. *Bathochromic shifts* (D *and* H *bands*) *for methyl substitution, calculated conjugating powers, and free-valence numbers for* 1 : 2-*benzanthracene.*

Position	Δ_D (in Å)	Δ_H (in Å)	Self-polarisability [a] (M.O. Method)	Free-valence number [b] (M.O. Method)	Free-valence number [c] (V. B. Method)
3'	15	25	0·404	0·352	0·164
6	15	25	0·409	0·355	0·168
7	10	−5	0·410	0·356	0·168
2'	35	15	0·410	0·357	0·171
1'	5	0	0·429	0·388	0·181
4'	55	35	0·439	0·399	0·192
4	15	10	0·441	0·403	0·200
8	30	50	0·449	0·404	0·196
3	35	−5	0·449	0·404	0·204
5	20	50	0·452	0·406	0·198
9	35	105	0·495	0·484	0·241
10	40	135	0·513	0·462	0·255

[a] These values should be multiplied by $1/\beta$. [b] Berthier, Coulson, Greenwood, and Pullman, *Compt. rend.*, 1948, **226**, 1906. [c] Pullman, *Ann. Chim.*, 1947, **2**, 5.

Three of the compounds in the present series (2'-, 3-, and 7-methyl-1 : 2-benzanthracenes) show a curious set of intermediate bands in the group-II region (see Fig. 2). These subsidiary bands are separated from the main bands by approximately 700 cm.$^{-1}$, and their origin is obscure. However, similar duplication of bands with methyl substitution has sometimes been observed in other cases, *e.g.*, in the visible spectrum of 2-methylazulene, but not in the spectra of the other methylazulenes (Plattner, *Helv. Chim. Acta*, 1941, **24**, 283E).

It is difficult to estimate the bathochromic shifts with any great accuracy. Some of the bands are relatively broad or irregular in shape, and it is not always possible to identify the complete set. In these circumstances, it has been thought best to study the shifts of the *D* and *H* bands only, especially as Jones (*loc. cit.*; *Chem. Reviews*, 1943, **32**, 1) has already examined the shifts in these bands produced by the six isomers previousy studied. The complete set of shifts is given in Table 2. The results certainly indicate that the 9- and

the 10-position have the greatest conjugating power. With less certainty it may be said that the 2′-, 4′-, 3-, 5-, and 8-positions all have a moderate conjugating power, and that the remaining positions have relatively small conjugating power. The 1′- and the 4-isomer show smaller bathochromic shifts than expected; but in the former this may be due to steric effects.

It is instructive to compare these results with the quantitative estimates of the conjugating powers of the various positions as calculated by the method of molecular orbitals.

FIG. 1. *Absorption spectrum of 1 : 2-benzanthracene.*

FIG. 2. *Absorption spectrum of 2′-methyl-1 : 2-benzanthracene.*

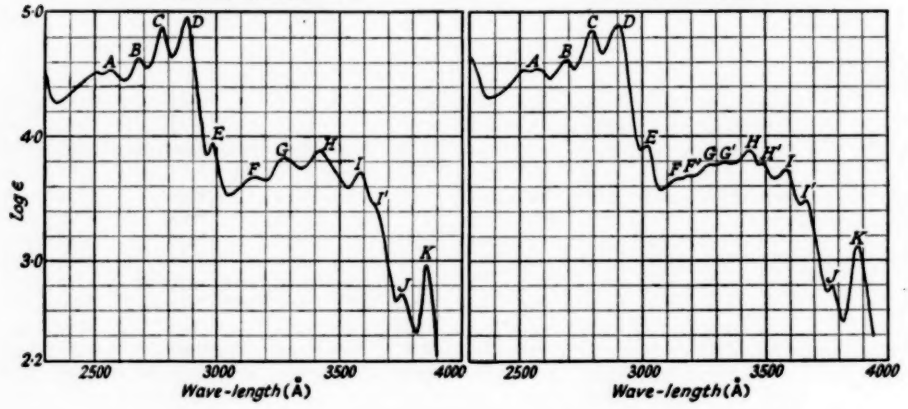
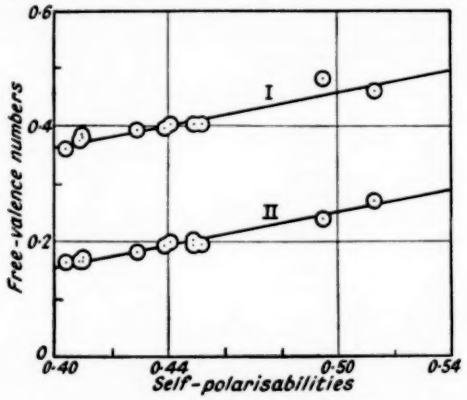


FIG. 3. *Curves showing the relationship between self-polarisabilities and free-valence numbers, M.O. method (curve* I*), and between self-polarisabilities and free-valence numbers, V. B. method (curve* II*).*



According to the treatment elaborated by Coulson and Longuet-Higgins (*Proc. Roy. Soc.*, *A*, 1947, **191**, 39; 1948, **195**, 188) the conjugating power of a given position is defined as β times the self-polarisability of that position. The self polarisability (π_{rr}) in an alternant hydrocarbon is given by the expression :

$$\pi_{rr} = 4 \sum_{j=1}^{n} \sum_{k=1}^{n} \frac{c_{rj}^2 \, c_{rk}^2}{\varepsilon_j + \varepsilon_k}$$

where n is the number of occupied orbitals, c_{rj} (c_{rk}) is the coefficient of the atomic orbital r occurring in the j th (k th) molecular orbital and ε_j (ε_k) the difference in energy of the j th (k th) molecular orbital from H_{cc}, the coulomb integral for the carbon atom in, say, benzene.

The values of π_{rr} for the twelve positions in 1 : 2-benzanthracene have now been calculated and have been included in Table 2. There the compounds are arranged in increasing order of the positions as determined by this method. In view of the inaccuracies of the spectrographic method, no perfect correlation between self-polarizability and bathochromic shift can be expected, but with one or two exceptions a rough qualitative correlation does appear to exist. In particular, both methods indicate that the 9- and the 10-position have the greatest conjugating power.

Some studies have already been published on the relation between conjugating power and the free-valence number of a given position as determined by the valence-bond method. For example, B. Pullman (*Compt. rend.*, 1946, **222**, 1396) has pointed out that the extent of hyperconjugation of a methyl substituent is dependent on the free-valence number, and that the greater the free-valence number, the greater the conjugation. This has recently been supported by some work by Daudel (*Compt. rend.*, 1950, **230**, 99) who has shown that there is a linear relation between the free-valence numbers (as determined by the method of spin states) and the bond orders of the bonds linking the substituent to the various positions of substitution. A similar relation between the extent of conjugation and the free-valence number as determined by the method of molecular orbitals must also be expected for it can be shown that there is a smooth-curve relation between the free-valence numbers as determined by the V. B. and M.O. methods.

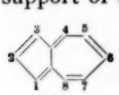
It is also noteworthy that A. Pullman (*Compt. rend.*, 1947, **224**, 1354; see also B. Pullman, *Bull. Soc. chim.*, 1948, **15**, 533) has found (for five monomethylbenzanthracenes) that there is an approximate correlation between the bathochromic shifts for methyl substitution and the " index of conjugation."

These relations all fall into place quite naturally when it is recognised that there are linear relations between the self-polarisabilities and the valence-bond free-valence numbers on the one hand, and between the self-polarisabilities and the M.O. free-valence numbers on the other. These linear relations are illustrated by Fig. 3, in which the various values for all twelve substitution positions are plotted.

TABLE 3. *Comparison between π-electron densities, and the observed shifts in the longest-wave-length band in the visible region when azulene is alkylated.*

Position of methyl group	π-Electron density	Observed shift ($cm.^{-1}$)	Position of methyl group	π-Electron density	Observed shift ($cm.^{-1}$)
1	1·173	−800	5	0·986	−360
2	1·047	+440	6	0·870	+380
3	1·173	−800	7	0·986	−360
4	0·855	+360	8	0·855	+360

In conclusion, reference may be made to the study of the bathochromic and hypsochromic shifts produced by methyl substitution in non-alternant aromatic hydrocarbons and in aromatic heterocyclic compounds. In these compounds, the annular carbon atoms normally have π-electron densities which are either greater than, or less than, unity. Brown and Lahey (*Austral. J. Sci. Res.*, 1950, **3**, *A*, 593) have claimed that a bathochromic shift is produced if the substituent is present in a position of (locally) high π-electron density, and that a hypsochromic shift is produced if the same substituent is present in a position of (locally) low π-electron density. They cite the case of the methylazulenes in support of the generalisation, but we believe that no such correlation exists in this case.


(II)

Methyl substitution in the 1-, 3-, 5-, and 7-positions of azulene (II) (not the 1-, 5-, and 7-, as stated) shifts the visible absorption bands to longer wave-lengths, and similar substitution in the 2-, 4-, 6-, and 8-positions (not 2-, 3-, 6-, and 8-, as stated) has been shown to shift the visible absorption bands in the opposite direction (Plattner, *loc. cit.*; see also Haagen-Smit, " Fortschritte der Chemie Organischer Naturstoffe," Springer-Verlag, Vol. 5, 1948, p. 40). The extent of shift for the absorption band of longest wave-length is given in Table 3, which also includes the π-electron densities of the various positions as calculated by Brown (*Trans. Faraday Soc.*, 1948, **44**, 984). There seems to be no correlation between the two sets of figures. (The work of Pullman, Mayot, and Berthier, *J. Chem. Phys.*, 1950, **18**,

257, and of Mann, Platt, and Klevens, *ibid.*, 1949, **17**, 481, however, does appear to offer an explanation for the observed shifts.)

It is interesting that in the *ultra-violet* part of the spectrum, the shifts are *always* to longer wave-length whatever the position of substitution, and it may be significant that the greatest shifts are produced by substitution in the 1-, 2-, and 3-positions, which have high π-electron densities (Plattner and Heilbronner, *Helv. Chim. Acta*, 1948, **31**, 804).

Experimental.—The ultra-violet absorption spectra were determined, in absolute ethanol, by means of a Hilger Uvispek Spectrophotometer.

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UNIVERSITY OF ADELAIDE. [*Received, November 7th*, 1951.]

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196. *Some Observations on the Course of the Reaction between Ethylenic Compounds and* N-*Bromosuccinimide.*

By E. A. BRAUDE and E. S. WAIGHT.

The reaction between *N*-halogenoimides and ethylenic compounds appears to involve two competing processes, leading to allylic substitution and halogen addition, respectively. Normally, substitution is predominant (Ziegler), but certain structural features promote addition which becomes the main reaction in the case of *cyclo*butene (Howton). Addition can also be promoted by certain catalysts; thus, whereas the action of *N*-bromosuccinimide on *cyclo*hexene ordinarily gives 3-bromo*cyclo*hexene, in the presence of alkylammonium salts 1 : 2-dibromo*cyclo*hexane is the major product. It is suggested that whereas substitution involves homolytic fission of the N–Br bond (Bloomfield), addition involves heterolytic fission which can be aided by complex formation with the *N*-halogenoimide. Addition compounds of *N*-bromosuccinimide and tetra-alkylammonium halides have been isolated.

The action of *N*-bromosuccinimide on allylbenzene results mainly in substitution, accompanied by allylic rearrangement, to give cinnamyl bromide. In the presence of triethylamine, however, which is rapidly converted into triethylamine hydrobromide, mainly 1 : 2-dibromo-3-phenylpropane is obtained. The action of 2 : 4 : *N*-trichloroacetanilide, even in the absence of salts, gives a mixture of substitution and addition products.

The action of *N*-bromosuccinimide on allylhexyne results mainly in substitution, accompanied by rearrangement, to give 1-bromonon-2-en-4-yne.

IT was first shown by Ziegler and his co-workers (*Annalen*, 1942, **551**, 80) that *N*-bromosuccinimide and *cyclo*hexene give mainly 3-bromo*cyclo*hexene and succinimide. Allylic bromination of this type has since become a widely employed preparative method (for an excellent summary, see Djerassi, *Chem. Reviews*, 1948, **43**, 271) and it is now generally accepted that it involves homolytic fission of the N–Br bond. The assumption of a free-radical mechanism is supported, *inter alia*, by the fact that allylic bromination is catalysed by peroxides (Karrer and Schmid, *Helv. Chim. Acta*, 1946, **29**, 525) and promoted by illumination (Meystre and Miescher, *ibid.*, 1945, **28**, 1497; 1946, **29**, 33). A detailed reaction scheme has been put forward (Bloomfield, *J.*, 1944, 114) which involves (i) homolytic fission into $(CH_2{\cdot}CO)_2N{\cdot}$ and Br·, (ii) abstraction of a hydrogen atom from the allyl position of the olefin by $(CH_2{\cdot}CO)_2N{\cdot}$, and (iii) reaction between the resulting allyl radical and bromosuccinimide to give the allylic bromide and $(CH_2{\cdot}CO)_2N{\cdot}$, followed again by (ii) in a chain process.

Reaction between N-*Bromosuccinimide and* cyclo*Hexene.*—In connection with other work, a closer study has been made of the products of the reaction between *N*-bromosuccinimide and *cyclo*hexene (cf. Braude and Waight, *Nature*, 1949, **164**, 241). Using excess of *cyclo*hexene and carbon tetrachloride as a diluent, Ziegler and his co-workers

(*loc. cit.*) obtained almost theoretical yields (based on the bromo-imide) of succinimide, and 80—90% yields of 3-bromo*cyclo*hexene, together with small amounts of undistilled residues. More recently, Howton (*J. Amer. Chem. Soc.*, 1947, **69**, 2060) carried out the reaction in benzene and isolated, besides 3-bromo*cyclo*hexene (50%), 1 : 2-dibromo*cyclo*hexane (15%) and small quantities of 3 : 6-dibromo*cyclo*hexene and *N*-phenylsuccinimide. We find that appreciable proportions of 1 : 2-dibromo*cyclo*hexane are also formed in light petroleum or chloroform; moreover, the yields of 3-bromo*cyclo*hexene are markedly lower, and those of the saturated dibromide are higher, on addition of alkylammonium salts and, to a smaller extent, of inorganic salts (see Table). The same effect can be produced by the addition of triethylamine; separate experiments showed that triethylamine rapidly reacted with *N*-bromosuccinimide to give succinimide and triethylamine hydrobromide. It will be noted that, unlike the substitution reaction (*S*), the addition reaction (*A*) requires the provision of two extra hydrogen atoms which are presumably derived either from part of the *cyclo*hexene or from the solvent.

$$(S)\quad C_6H_{10} + (CH_2{\cdot}CO)_2NBr \longrightarrow C_6H_9Br + (CH_2{\cdot}CO)_2NH$$

$$(A)\quad C_6H_{10} + 2(CH_2{\cdot}CO)_2NBr \xrightarrow{2H} C_6H_{10}Br_2 + 2(CH_2{\cdot}CO)_2NH$$

Bromination of cyclo*hexene with* N-*bromosuccinimide in chloroform.*

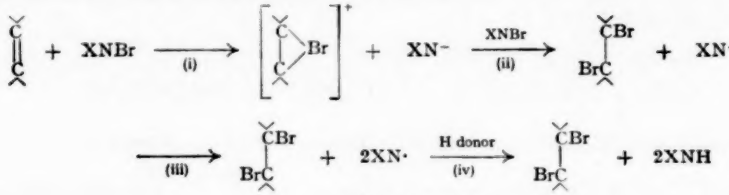
Catalyst	Mol. propn.*	Yield (%) * of 3-bromo*cyclo*hexene	Yield (%) * of 1 : 2-dibromo*cyclo*hexane
—	—	30	12
LiCl	0·5	30	20
KCl	0·25	31	31
NEt_3	0·1	18	36
NEt_3,HBr	0·2	4	50
NEt_4Br	0·4	2	74
NEt_4I	0·4	3	62

* Based on *N*-bromosuccinimide.

The formation of saturated dibromo-derivatives, sometimes as major products, has also been observed in several other cases, *e.g.*, in the reaction between *N*-bromosuccinimide and 3-β-acetoxy-24 : 24-diphenyl*allo*chol-23-ene (Wieland and Miescher, *Helv. Chim. Acta*, 1947, **30**, 1876), *cyclo*butene and methylene*cyclo*butane (Buchmann and Howton, *J. Amer. Chem. Soc.*, 1948, **70**, 2517, 3510), ethyl tetrolate (English and Gregory, *ibid.*, 1949, **71**, 1115), methyl and phenyl styryl ketone (Southwick, Pursglove, and Numerof, *ibid.*, 1950, **72**, 1600), and allyl cyanide (Waight, Thesis, London, 1950), between *N*-bromophthalimide and *cyclo*hexene (Ziegler *et al.*, *loc. cit.*), and between *N*-bromoacetamide and stilbene (Buckles, *J. Amer. Chem. Soc.*, 1949, **71**, 1157). It thus appears that the addition reaction generally competes to some extent with the more usual substitution reaction and that the balance between the two reactions depends (*a*) on the structure of the *N*-halogeno-compound, (*b*) on the structure of the olefin, (*c*) on the solvent and experimental conditions, and (*d*) on the presence of certain catalysts, such as alkylammonium salts, which promote the addition reaction.

It was suggested by Wieland and Miescher (*loc. cit.*) that the addition reaction is due to free bromine, liberated by the interaction of *N*-bromosuccinimide and hydrogen bromide formed by side reactions such as dehydrohalogenation of the allylic bromide. No hydrogen bromide or bromine are observed, however, in the reactions described above. 3-Bromo-*cyclo*hexene is recovered largely unchanged after treatment with tetraethylammonium bromide in boiling chloroform, and no easily detectable amount of bromine is liberated in a boiling solution of *N*-bromosuccinimide and triethylamine hydrobromide in chloroform. Further convincing evidence against the intervention of free bromine has been adduced by Southwick *et al.* (*loc. cit.*) and there can be no doubt that the addition reaction involves the direct interaction between the *N*-halogeno-compound and the olefin. In some of the cases reported by Buckles and by Southwick, the addition reactions are accelerated by peroxides and light and appear to be radical reactions, like allylic substitution. The salt-catalysed nature of the bromine-addition reactions of *N*-bromosuccinimide with *cyclo*hexene and also with allylbenzene (see below), however, suggests the possibility that they may involve

heterolytic rather than homolytic fission of the N–Br bond as the primary and rate-determining step, although the formation of succinimide undoubtedly involves a subsequent homolytic hydrogen abstraction. A similar conclusion was reached by Buckles (*loc. cit.*) who found that, whereas the peroxide-catalysed reaction of *cis*-stilbene with *N*-bromoacetamide yielded *meso*stilbene dibromide, in the presence of hydrogen bromide the product was racemic stilbene dibromide. That the homolytic and the heterolytic mode of fission take place with comparable ease is indicated by the ionic reactions which *N*-halogeno-compounds undergo in polar solvents (cf. Winstein and Lucas, *J. Amer. Chem. Soc.*, 1939, **61**, 1576; Raphael, *J.*, 1949, S 44) and is understandable in view of the low bond energy (*ca.* 33 kcal./mole) and very similar electronegativities (3·0 and 2·8; Pauling, "The Nature of the Chemical Bond," New York, 1940) of nitrogen and bromine. A plausible mechanism for the addition reaction is as follows:



[X = $(CH_2 \cdot CO)_2$.]

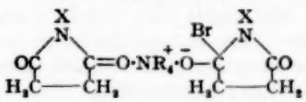
The first step is the slow reaction with the olefin to give the bromonium ion and a succinimide anion. Reaction (ii) gives the dibromo-compound and a succinimide cation. The two succinimide ions then undergo electron-transfer and are converted into two succinimidyl radicals; finally, each radical abstracts a hydrogen atom from a donor. The first step is entirely analogous to that generally accepted for the addition of bromine itself to olefins (cf. Roberts and Kimball, *J. Amer. Chem. Soc.*, 1937, **59**, 947; De La Mare, *Quart. Reviews*, 1949, **3**, 126). As would be expected from step (ii), the 1 : 2-dibromo*cyclo*hexane formed appears to be the *trans*-isomer, identical in physical properties with that obtained by the addition of bromine itself to *cyclo*hexene (Winstein, *J. Amer. Chem. Soc.*, 1942, **64**, 2792). The fact that the addition is completed by reaction with a second molecule of bromoimide rather than by the formation of the 1-bromo-2-succinimido-derivative is comprehensible in terms of the relative strengths of the C–N, C–Br and N–Br bonds and by analogy with ordinary addition, which frequently involves concerted attack by two or more molecules of halogen (cf. De La Mare, *loc. cit.*; De La Mare and Robertson, *J.*, 1950, 2838). It is of interest in this connection, however, that 1-bromo-2-phthalimido*cyclo*hexane is obtained as a by-product in the reaction between *N*-bromophthalimide and *cyclo*hexene (Ziegler *et al.*, *loc. cit.*). Step (iii) might perhaps be expected to yield the unknown disuccinimidyl XN·NX, but attempts to prepare this compound by the reaction of *N*-bromosuccinimide with silver succinimide or mercury were unsuccessful (see Experimental) and this compound is evidently very unstable, probably dissociating with ease into two succinimidyl radicals. Thus, step (iii) in the above scheme is a reasonable hypothesis. Step (iv) is entirely analogous to the hydrogen abstraction involved in the substitution reaction (Bloomfield, *loc. cit.*). Although some of the intermediates above have been written as separate ions for clarity, steps (i) and (ii) may represent partial rather than complete electron-transfers and the bromonium and succinimide ions undoubtedly remain in their mutual spheres of influence until step (iii) is complete. This is also indicated by the fact that no iodine-containing products are obtained when the reaction is carried out in the presence of tetraethylammonium iodide.

The two modes of reaction of *N*-bromosuccinimide with olefins are paralleled by two corresponding modes of reaction with aromatic compounds. Thus, it has been shown by Schmid (*Helv. Chim. Acta*, 1946, **29**, 1144) that toluene reacts with *N*-bromosuccinimide in the presence of benzoyl peroxide to give benzyl bromide, whereas in the presence of aluminium trichloride and similar catalysts a mixture of bromotoluenes is formed. Side-chain bromination is, of course, analogous to allylic substitution, while nuclear bromination

is analogous to olefin addition (cf. Braude, *Ann. Reports*, 1949, **46**, 138) and almost certainly proceeds by an ionic mechanism. Attempts to investigate the effects of aluminium trichloride on the reaction between *cyclo*hexene and *N*-bromosuccinimide were unsuccessful because of the explosive nature of the reaction mixture.

The influence of the structure of the olefin and of the *N*-halogeno-compounds fits in with the idea of competing homolytic substitution and heterolytic addition reactions. Addition is favoured by olefinic compounds in which the ethylenic system is either relatively unstable thermodynamically, as in *cyclo*butene, or highly polarised, as in phenyl styryl ketone. Similarly, addition is more pronounced with those *N*-halogeno-compounds which are less reactive in allylic substitution, *i.e.*, in which the *N*–halogen bond is more polar.

The question arises as to the mode of functioning of alkylammonium salts in promoting the addition reaction. Several ways can be envisaged, *e.g.*, (*a*) inhibition of the radical reaction by chain-breaking or (*b*) facilitation of the heterolytic fission of the N–Br bond, either (i) indirectly by the increase in the ionising properties of the solvent, or directly by association with (ii) the *N*-halogeno-compound or (iii) the olefin. The first way seems the least likely, *inter alia*, because tetraethylammonium bromide is more effective than triethylamine hydrobromide which might be expected to be the better radical-chain inhibitor. Amongst the other possibilities, (*b*, i) alone also seems improbable since the alkylammonium salts will exist largely as undissociated ion-pairs in the organic solvents, while the inorganic salts are practically insoluble, so that the change in ionic strength will be small. Association between alkylammonium cations and the olefin may take place, analogous to the π-complex formation observed with many other cations (cf. Winstein and Lucas, *J. Amer. Chem. Soc.*, 1938, **60**, 836; Dewar, *J.*, 1946, 406); this would, however, facilitate nucleophilic rather than electrophilic attack, and (*b*, ii) would therefore require a reversal of the sequence of steps (i) and (ii) in the reaction scheme above. The most likely explanation appears to be (*b*, iii); association between *N*-bromosuccinimide and tetraethylammonium bromide and iodide almost certainly occurs since unstable addition compounds, as well as a more stable adduct with succinimide, can be isolated. The nature of the addition compounds has not been elucidated, but any interaction of this kind will undoubtedly increase the ionic character of the N–Br bond and facilitate steps (i) and (ii) in the addition reaction. The adducts all contain two molecules of imide and one molecule of tetra-alkylammonium salt, and a possible formulation is that shown below in which the carbonyl group of one imide molecule acts as a base and the carbonyl group of the other as an acid :



Reaction between N-*Halogenoimides and Allylbenzene.*—Several instances have been described of allylic rearrangement accompanying the reactions of *N*-bromosuccinimide with ethylenic compounds (*inter alia*, Djerassi, *loc. cit.*; Karrer and his co-workers, *Helv. Chim. Acta*, 1947, **30**, 863, 1771; 1948, **31**, 395; Bateman, Cunneen, Fabian, and Koch, *J.*, 1950, 936; Bateman and Cunneen, *ibid.*, p. 941; Gensler, *J. Amer. Chem. Soc.*, 1951, **73**, 1071; Barnes and Buckwalter, *ibid.*, p. 3858). The occurrence of rearrangement is compatible with the generally accepted view that such reactions involve the intervention of allylic radicals, since the latter will be subject to electron-resonance and will give rise to mixtures of products depending on the relative contributions of structures such as X·ĊH·CH:CHY and X·CH:CH·ĊHY to the hybrid radical. As has been pointed out by Bateman *et al.* (*loc. cit.*), however, the production of isomeric bromides is often to be expected quite independently of their mode of formation, since allylic bromides are known to undergo isomerisation with ease, most probably by a homolytic mechanism (for references see Braude, *Ann. Reports*, 1949, **46**, 129; *Quart. Reviews*, 1950, **4**, 404).

Most of the cases in which rearrangement accompanying halogenation has so far been observed relate to derivatives containing only alkyl substituents directly attached to the allyl grouping; in such circumstances the difference in energy content of the two isomers is relatively small and the equilibrium mixture contains isolatable proportions of both

bromides at ordinary temperatures. In allyl derivatives containing an unsaturated substituent, on the other hand, the equilibrium will be far on one side owing to the extra resonance energy associated with a conjugated system and it would therefore be expected that the halogenation of compounds such as allylbenzene (I) will be accompanied by almost complete rearrangement. Since 1-phenylallyl bromide and similar bromides are unknown, it appeared desirable to confirm this expectation, particularly in view of the fact that certain other reactions believed to involve phenylallyl radicals have been reported to furnish mixtures containing as much as 25% of the unconjugated 1-phenylallyl derivatives (Kharasch, Lambert, and Urry, *J. Org. Chem.*, 1945, **10**, 298; Koch, *J.*, 1948, 1111).

The reaction of *N*-bromosuccinimide with allylbenzene, like that with propenylbenzene (Ziegler *et al.*, *loc. cit.*), proceeds very slowly in dilute carbon tetrachloride solution, but is greatly accelerated by benzoyl peroxide. The main product (50%) is cinnamyl bromide (II), identified by its melting point and ultra-violet light-absorption ($\lambda_{max.}$ 2590 Å, ε 17000).

$$\underset{\text{(IV)}}{\text{Ph}\cdot\text{CH}_2\cdot\text{CHBr}\cdot\text{CH}_2\text{Br}} \longleftarrow \underset{\text{(I)}}{\text{Ph}\cdot\text{CH}_2\cdot\text{CH}{:}\text{CH}_2} \longrightarrow \underset{\text{(II)}}{\text{Ph}\cdot\text{CH}{:}\text{CH}\cdot\text{CH}_2\text{Br}} \longrightarrow \underset{\text{(III)}}{\text{Ph}\cdot\text{CHBr}\cdot\text{CH}{:}\text{CH}_2}$$

1-Phenylallyl bromide (III) would only exhibit low-intensity absorption in this region and it can be estimated from the spectral data for the crude distillable products that less than 10% of unconjugated bromide was present, if any. Since the preliminary report of this work (*Nature*, 1949, **164**, 241) a similar conclusion has been reached by Lora-Tamayo, Martin-Panzio, and Perez Ossorio (*J.*, 1950, 1418), though on rather less secure evidence.

Similar results are obtained when the reaction is carried out in light petroleum (b.p. 80—100°) either in the presence of benzoyl peroxide or on irradiation with ultra-violet light. The course of the bromination is completely altered, however, on the addition of catalytic quantities of triethylamine, which is rapidly converted into triethylamine hydrobromide by *N*-bromosuccinimide (see above) Under these conditions, the main product is, not cinnamyl bromide, but 1 : 2-dibromo-3-phenylpropane (IV), analogously to the "salt-catalysed" formation of dibromo*cyclo*hexane from *cyclo*hexene and *N*-bromosuccinimide.

Unlike allyl bromides, allyl chlorides do not readily isomerise (cf. Braude, *loc. cit.*). In order to test whether the extent of rearrangement in the halogenation of allylbenzene is dependent on the entering halogen radical, the reaction of the hydrocarbon with 2 : 4 : *N*-trichloroacetanilide (cf. Ziegler *et al.*, *loc. cit.*) was examined. Under the conditions employed for the bromination, this yields very slowly a mixture of cinnamyl chloride and 1 : 2-dichloro-3-phenylpropane. The two products are not readily separable by fractionation on a small scale, but the analytical data indicate that the proportion of any 1-phenylallyl chloride present amounted to less than 10%.

Reaction between N-*Bromosuccinimide and Allylhexyne.*—As a further example, the bromination of allylhexyne (non-1-en-4-yne) (V) with *N*-bromosuccinimide has been carried out. This is much slower than that of allylbenzene: even in the presence of benzoyl peroxide, a large proportion of the hydrocarbon is recovered unchanged after 20 hours in boiling carbon tetrachloride. As in the previous case, the substitution reaction is

$$\underset{\text{(V)}}{\text{Bu}^n\cdot\text{C}{\equiv}\text{C}\cdot\text{CH}_2\cdot\text{CH}{:}\text{CH}_2} \qquad \underset{\text{(VI)}}{\text{Bu}^n\cdot\text{C}{\equiv}\text{C}\cdot\text{CH}{:}\text{CH}\cdot\text{CH}_2\text{Br}}$$

accompanied by extensive, though not necessarily complete, isomerisation. The main product isolated is the primary bromide (VI), which exhibits ultra-violet light absorption properties typical of a conjugated vinylacetylene and was converted, by alkaline hydrolysis and catalytic hydrogenation, into nonyl alcohol, identified as the 3 : 5-dinitrobenzoate. The only other recorded example of the halogenation of an acetylenic derivative with *N*-bromosuccinimide appears to be that of ethyl tetrolate which undergoes addition to give ethyl $\alpha\beta$-dibromocrotonate rather than allylic substitution (English and Gregory, *J. Amer. Chem. Soc.*, 1949, **71**, 1115).

Experimental

Bromination of cyclo*Hexene.*—*N*-Bromosuccinimide (crystallised from boiling water and vacuum-dried) was added to the solvent containing the catalyst (if any) and, after any ensuing reaction was complete, *cyclo*hexene was added. The mixture was then heated under reflux

for 20—60 minutes, cooled, and filtered. The residue (A) was extracted with more solvent, and the combined filtrate and washings were concentrated by distillation and then diluted with carbon tetrachloride, if necessary, to precipitate more succinimide and alkylammonium salts which were filtered off (B). The remaining solution was fractionated under reduced pressure, and the proportions of 3-bromo*cyclo*hexene (n_D^{20} 1·5270) and 1 : 2-dibromo*cyclo*hexane (n_D^{20} 1·5516) were estimated by refractive-index measurements. In some cases, the two bromo-compounds were also separated by treatment with triethylamine, 3-bromo*cyclo*hexene giving a quaternary salt, m. p. 197° (cf. Howton, *loc. cit.*). The residues (A) and (B) were combined and succinimide was isolated from them by extraction with acetone or benzene–ethanol. Three typical experiments are recorded below.

(*a*) A mixture of *N*-bromosuccinimide (22 g.), potassium chloride (3·5 g.), *cyclo*hexene (10 g.), and chloroform (50 ml.) was heated under reflux for 1 hour. Working up as described gave succinimide, m. p. 123° (18 g., 90%), and a mixture of bromination products which was separated into fractions: (i) b. p. 76—90°/14 mm., n_D^{20} 1·5255 (3·3 g.), (ii) b. p. 90—96°/14 mm., n_D^{20} 1·5379 (5·7 g.), and (iii) b. p. 96—102°/14 mm., n_D^{20} 1·5425 (8·4 g.); this represents a total yield of 9·9 g. (31%) of 3-bromo*cyclo*hexene and 7·5 g. (31%) of 1 : 2-dibromo*cyclo*hexane.

(*b*) A mixture of *N*-bromosuccinimide (25 g.), tetraethylammonium bromide (13 g.), *cyclo*hexene (16 g.), and chloroform (70 ml.) was heated under reflux for 20 minutes. Working up as above gave fractions: (i) b. p. 102—106°/18 mm., n_D^{20} 1·5450 (1·8 g.), (ii) b. p. 106—107°/18 mm., n_D^{20} 1·5502 (6 g.), and (iii) b. p. 107—109°/18 mm., n_D^{20} 1·5510 (5 g.) (Found: Br, 65·6. Calc. for $C_6H_{10}Br_2$: Br, 66·1%), representing a total yield of 0·5 g. (2%) of 3-bromo*cyclo*hexene and 12·3 g. (74%) of dibromo*cyclo*hexane. The solid products contained succinimide and an addition *compound* of the latter with tetraethylammonium bromide which separated from ethanol in orange crystals, m. p. 170—171° (Found: C, 47·4; H, 7·6; N, 9·9; Br, 19·9. $2C_4H_5O_2N,C_8H_{20}NBr$ requires C, 47·1; H, 7·4; N, 10·3; Br, 19·6%).

(*c*) A mixture of *N*-bromosuccinimide (25 g.), tetraethylammonium iodide (15·5 g.), *cyclo*hexene (16 g.), and chloroform (100 ml.) was heated under reflux for 40 minutes. Working up as above gave fractions: (i) b. p. 44—45°/0·1 mm., n_D^{20} 1·5490 (6 g.), and (ii) b. p. 46—50°/0·1 mm., n_D^{20} 1·5506 (4·6 g.), representing a total yield of 0·6 g. (3%) of 3-bromo*cyclo*hexene and 10 g. (62%) of 1 : 2-dibromo*cyclo*hexane. Both fractions gave negative tests for iodine.

Bromination of Allylbenzene.—(*a*) A mixture of *N*-bromosuccinimide (20 g.), allylbenzene (13 g.), and carbon tetrachloride (130 ml.) was refluxed for 2 hours. Little reaction occurred and benzoyl peroxide (500 mg.) was added. After a further 2 hours' heating, the mixture was cooled and filtered. The residue consisted mainly of succinimide, m.p. 124° after crystallisation from methanol. The solution was distilled under reduced pressure. The fractions with b. p. 70—85°/0·05 mm., n_D^{20} 1·6100–6130, $\lambda_{max.}$ 2590 Å, $E_{1\,cm.}^{1\%}$ 730—830, were dissolved in pentane; on cooling, cinnamyl bromide (11 g., 50%), m. p. 28—30°, separated. Two further crystallisations raised the m.p. to 30°, undepressed on admixture with an authentic specimen prepared by the reaction of cinnamyl alcohol with phosphorus tribromide. The pure bromide had $\lambda_{max.}$ 2590 ($E_{1\,cm.}^{1\%}$ 850) and 2640 Å ($E_{1\,cm.}^{1\%}$ 820) in hexane.

(*b*) A mixture of *N*-bromosuccinimide (9 g.), allylbenzene (12 g.), and light petroleum (b. p. 80—100°; 100 ml.) was heated under reflux in a "Pyrex" flask irradiated with a mercury arc. Distillation afforded cinnamyl bromide (7 g., 70% based on *N*-bromosuccinimide), b. p. 51—52°/0·005 mm., n_D^{20} 1·6130—1·6150, m. p. 30° after one crystallisation from pentane.

(*c*) *N*-Bromosuccinimide (31 g.) was added portionwise to a solution of allylbenzene (21 g.) and triethylamine (1·7 g.) in light petroleum (b. p. 80—100°; 200 ml.). Benzoyl peroxide (500 mg.) was then added and the mixture was heated under reflux for 30 minutes. After filtration, most of the solvent was distilled off, N-acetic acid (100 ml.) was added, and the resulting solution was extracted with ether. Distillation of the extract through a short Fenske column afforded unchanged allylbenzene (10 g.), and dibromophenylpropane (10·6 g., 44% based on *N*-bromosuccinimide), b. p. 76—78°/0·05 mm., n_D^{20} 1·5860, $\lambda_{max.}$ 2590 ($E_{1\,cm.}^{1\%}$ = 28) (Found: C, 39·6; H, 3·9; Br, 56·6. Calc. for $C_9H_{10}Br_2$: C, 38·9; H, 3·6; Br, 57·5%). An authentic sample, prepared by the addition of bromine to allylbenzene in carbon tetrachloride, had b. p. 78°/0·05 mm., n_D^{20} 1·5857.

Chlorination of Allylbenzene.—2 : 4 : *N*-Trichloroacetanilide was prepared by adding a solution of acetanilide in acetic acid to 15% aqueous sodium hypochlorite solution and, after crystallisation from chloroform–light petroleum, had m. p. 68—71°, not raised by further treatment with hypochlorite (Chattaway and Orton, *J.*, 1899, 1052, give m. p. 77°). A mixture of the chloro-amine (20 g.), allylbenzene (10 g.), carbon tetrachloride (100 ml.), and benzoyl peroxide (500 mg.) was heated under reflux for 60 hours. After cooling and filtering, the liquid products

were distilled, giving unchanged allylbenzene (6 g.) and a mixture of chlorinated hydrocarbons (3 g.), b. p. 68—72°/0·6 mm., n_D^{21} 1·5686. Analytical data (total Cl, 26·8; Cl, hydrolysable by aqueous potassium carbonate, 16·0%; $\lambda_{max.}$ 2550 Å., $E_{1\,cm.}^{1\%}$ 1000. Calc. for cinnamyl chloride: Cl, 23·3%; $E_{1\,cm.}^{1\%}$ 1300) indicate that the latter consisted of cinnamyl chloride (*ca.* 70%) and 1 : 2-dichloro-3-phenylpropane (30%).

Bromination of Allylhexyne.—A mixture of *N*-bromosuccinimide (18 g.), allylhexyne (12·5 g.; Danehy, Killian, and Nieuwland, *J. Amer. Chem. Soc.*, 1936, **58**, 611), carbon tetrachloride (50 ml.) and benzoyl peroxide (500 mg.) was heated under reflux for 10 hours. After cooling, the mixture was filtered and distilled, giving unchanged allylhexyne (8 g.) and 1-*bromonon-2-en-4-yne* (3 g.), b. p. 63—64°/0·4 mm., n_D^{21} 1·5145 (Found: Br, 40·3. $C_9H_{13}Br$ requires Br, 39·9%). Light absorption in hexane: $\lambda_{max.}$ 2420 and 2490 Å (ε 8000). The bromide was refluxed with sodium carbonate (1·5 g.) in aqueous acetone, and the resulting carbinol (1·5 g.), b. p. 84—88°/1·5 mm., $\lambda_{max.}$ 2280 Å (ε 12 000) was hydrogenated in methanol in the presence of a platinum catalyst, giving nonyl alcohol, b. p. 98°/8 mm., n_D^{20} 1·4301, which was identified as the 3 : 5-dinitrobenzoate, m. p. 52—53° (from methanol), undepressed on admixture with an authentic specimen. The latter was obtained from a sample of nonyl alcohol (2·5 g., 55%) prepared by treating pelargonic acid (5 g.) with lithium aluminium hydride (2·5 g.) in ether at room temperature.

Reaction between N-*Bromosuccinimide and Triethylamine.*—*N*-Bromosuccinimide (6 g.) was added portionwise to a solution of triethylamine (7 g.) in carbon tetrachloride (20 ml.) at 0°. The crystalline solid which separated was filtered off and extracted with acetone. The residue was triethylamine hydrobromide (3 g.), m. p. 245—246°, undepressed on admixture with an authentic sample. The acetone solution was evaporated to dryness, giving succinimide (2·5 g.) which was crystallised from ethanol–light petroleum and had m. p. 123°, undepressed on admixture with an authentic specimen. The reaction between *N*-bromosuccinimide and triethylamine has previously been investigated by Cosgrove and Waters (*J.*, 1949, 907) who reported only the formation of succinimide together with traces of other materials, but the method of working up employed by these authors would have precluded the isolation of triethylamine hydrobromide.

Reaction between N-*Bromosuccinimide and Tetraethylammonium Halides.*—*N*-Bromosuccinimide (0·71 g.) and tetraethylammonium bromide (0·42 g.) were dissolved in hot chloroform (50 ml.). The solvent was evaporated and the resulting *adduct* was recrystallised several times from chloroform, giving fine, colourless crystals, m. p. 144° (Found: C, 33·8; H, 5·2; N, 7·4; Br, 42·8. $2C_4H_4O_2NBr,C_8H_{20}NBr$ requires C, 33·9; H, 4·95; N, 7·4; Br, 42·4%). The adduct is soluble in benzene and can be recovered unchanged. It is also soluble in water, and the aqueous solution gives a positive test for bromide anion but fails to liberate iodine from acidified potassium iodide solution (cf. *N*-bromosuccinimide).

A solution of *N*-bromosuccinimide (0·71 g.) and tetraethylammonium iodide (0·51 g.) in hot chloroform (50 ml.) on cooling deposited orange crystals of an adduct from which no succinimide could be extracted with benzene. Recrystallisation from chloroform or chloroform–benzene was attended by partial decomposition and gave pale orange crystals, m. p. 115—116° (Found: C, 30·6; H, 4·4; N, 6·15. $2C_4H_4O_2NBr,C_8H_{20}NI$ requires C, 31·3; H, 4·6; N, 6·85%).

Attempts to prepare Disuccinimidyl.—(*a*) Silver succinimide (6 g.), prepared by treating succinimide with aqueous ethanolic silver nitrate, was added to a suspension of *N*-bromosuccinimide (7 g.) in benzene (100 ml.). Mixing caused the solution to become red, and a neutral gas was evolved. The mixture was mechanically shaken in a stoppered flask for 20 hours and filtered. The residue was silver bromide (6·3 g., 100%). The solution on evaporation yielded a small quantity of succinimide and an intractable tar.

(*b*) From a similar experiment in which mercury was substituted for silver succinimide, the only product isolated was mercury succinimide which crystallised from boiling ethanol and had m. p. 336° [Found: N, 7·07. Calc. for $(C_4H_4O_2N)_2Hg$: N, 7·05%].

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197. *The Synthesis of Some 5-Alkyl-2-methylbenzoic Acids.*

By E. P. Taylor and G. E. Watts.

5-Ethyl-2-methyl-, 2-methyl-5-*n*-propyl-, and 5-*tert.*-butyl-2-methylbenzoic acids have been synthesised and their constitutions established. The bromination and Friedel–Crafts acetylation of *p*-ethyl-, *p*-*n*-propyl-, and *p*-*tert.*-butyl-toluene, and the Friedel–Crafts acetylation of *p*-*iso*propyltoluene, have been investigated. Unless conditions are carefully controlled, the acetylations result in the replacement of the higher alkyl group by the acetyl group. A novel method of carboxylation of Grignard reagents is described.

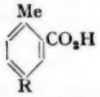
Of the alkyl-*o*-toluic acids (I—IV) required for the determination of their physical constants, only 2-methyl-5-*iso*propylbenzoic acid (III) had been prepared (Le Fèvre, *J.*, 1933, 983). However, certain of the intermediates necessary for the synthesis of the other three acids were known.

2-Amino-4-*tert.*-butyltoluene (Brady and Lahiri, *J.*, 1934, 1956) gave the 2-iodo-compound, which was converted into the carboxylic acid (IV) *via* its Grignard reagent. The synthesis was subsequently shortened, since bromination of *p*-*tert.*-butyltoluene gave 2-bromo-4-*tert.*-butyltoluene in good yield. The identity of the acid derived from this through its Grignard reagent with that obtained from the known 2-amino-derivative established the orientation of the bromination product. Thus, bromination of 4-*tert.*-butyltoluene, as might be expected, follows the same course as nitration.

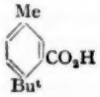
5-Ethyl-2-methylbenzoic acid (I) was obtained from 2-amino-4-ethyltoluene (Brady and Day, *J.*, 1934, 114) *via* the iodo-derivative. Bromination of *p*-ethyltoluene was first described by Remson and Morse (*Ber.*, 1878, **11**, 225) who claimed to have identified the product as the 2-bromo-derivative by its oxidation to 3-bromo-4-methylbenzoic acid. Defren (*Ber.*, 1895, **28**, 2651) also brominated *p*-ethyltoluene, without, however, establishing the constitution of the product. In the present work, bromination yielded a substance which, although boiling within a range of 1—2°, was apparently a mixture, since, on carboxylation of the Grignard reagent, an impure carboxylic acid resulted, which, even after several recrystallisations, still had an indefinite melting point, 20—30° lower than that of pure 5-ethyl-2-methylbenzoic acid. This is in agreement with the work of Brady and Day (*loc. cit.*), who showed that nitration of *p*-ethyltoluene yielded a mixture of 2- and 3-nitro-derivatives.

2-Methyl-5-*n*-propylbenzoic acid (II) was obtained from 4-methyl-3-nitropropiophenone (Errera, *Gazzetta*, 1891, **21**, I, 97), reduction of which, by the Clemmensen method, yielded 2-amino-4-*n*-propyltoluene in poor yield (cf. Brady and Day, *loc. cit.*, for the reduction of 4-methyl-3-nitroacetophenone); this readily gave the required acid by way of the iodo-compound and the Grignard reagent. Bromination of *p*-*n*-propyltoluene yielded a mono-bromo-derivative, shown to be the 2-bromo-compound by conversion through its Grignard reagent into 2-methyl-5-*n*-propylbenzoic acid identical with that previously prepared.

In all cases described above, a novel method of treatment with carbon dioxide under pressure was used, depending on preparation of the Grignard reagent in a strengthened glass vessel designed for making soda-water.



(I; R = Et)
(II; R = Pr^n)
(III; R = Pr^i)
(IV; R = Bu^t)



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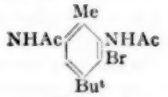

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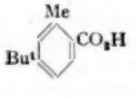
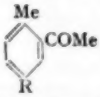


(VII)



(VIII; R = Et)
(IX; R = Pr^n)
(X; R = Pr^i)

Once the acids had been prepared and their orientation established, an alternative method of preparation appeared possible. This was to acetylate the *p*-alkyltoluenes by the Friedel–Crafts method, and to oxidise the resulting alkylmethylacetophenones by hypobromite. Comparatively little work appears to have been done on these acetylations.

Meissel (*Ber.*, 1899, **32**, 2422) reported that *p-tert.*-butyltoluene with acetyl chloride in the presence of anhydrous ferric chloride gave an acetyl-4-*tert.*-butyltoluene of undetermined orientation. Lacourt (*Bull. Soc. chim. Belg.*, 1929, **38**, 16), using aluminium chloride, reported an 80% yield of an unoriented acetyl-4-*tert.*-butyltoluene, with small quantities of *p*-methylacetophenone as a by-product. Claus (*J. pr. Chem.*, 1890, **42**, 508) and others (see Allen, *Org. Synth.*, Coll. Vol. II, John Wiley & Sons, 1943, p. 3) stated that Friedel–Crafts acetylation of *p*-cymene with acetyl chloride gave mainly 2-methyl-5-*iso*propyl-acetophenone, which has now been confirmed. No references were found to the acetylation of *p*-ethyl- or *p-n*-propyl-toluene.

In the present work acetic anhydride (1 mol.) was added to a mixture of *p-tert.*-butyltoluene (1 mol.) and anhydrous aluminium chloride (3—4 mols.) in carbon disulphide, with subsequent heating. *p*-Methylacetophenone, formed by the elimination of the *tert.*-butyl group, and a *tert.*-butylmethylacetophenone were obtained. Hypobromite oxidation of the latter yielded a *tert.*-butylmethylbenzoic acid melting at 144°, *i.e.*, considerably higher than 5-*tert.*-butyl-2-methylbenzoic acid (101°) and the mixed melting point was *ca.* 70—72°. Our acid was therefore at first assumed to be 2-*tert.*-butyl-5-methylbenzoic acid (V). In an attempt to confirm this, 4-*tert.*-butyl-2 : 6-dinitrotoluene (Brady and Lahiri, *J.*, 1934, 1955) was converted into 2 : 6-diacetamido-4-*tert.*-butyltoluene, which yielded a monobromo-derivative, necessarily 2 : 6-diacetamido-3-bromo-4-*tert.*-butyltoluene (VI). Numerous attempts at simultaneous elimination of the two amino-groups from this compound (after hydrolysis), to yield 3-bromo-4-*tert.*-butyltoluene were unsuccessful, and the attempted synthesis of (V) was therefore abandoned. From certain physical constants, determined later, it appears unlikely that the acid of m. p. 144° is 2-*tert.*-butyl-5-methylbenzoic acid, but probable that migration of the butyl group has occurred during acetylation. Baur-Thurgau (*Ber.*, 1900, **33**, 2569) describes 4-*tert.*-butyl-2-methylbenzoic acid (VII) of m. p. 140°, obtained by oxidation of 4-*tert.*-butyl-2-methylacetophenone.

Friedel–Crafts acetylation of *p*-ethyl- and *p-n*-propyl-toluene, under the experimental conditions described above, gave pairs of ketones, but only the lower-boiling ketone (*p*-methylacetophenone) could be isolated in the pure state. Aluminium chloride being a dealkylating agent, the experiments were repeated with acetyl chloride in place of acetic anhydride, since only one molecular proportion of aluminium chloride was then necessary. Under the same experimental conditions as before, *p*-methylacetophenone was again formed in considerable quantity. Finally, a mixture of the hydrocarbon (1 mol.) and acetyl chloride (1 mol.) was dropped into a stirred suspension of aluminium chloride (1 mol.) in carbon disulphide at room temperature. This was successful, in the cases of *p*-ethyl-, *p-n*-propyl-, *p-iso*propyl-, and *p-tert.*-butyl-toluene, in avoiding the formation of 4-methyl-acetophenone, whilst giving the acetyl derivatives of the hydrocarbons in good yield.

As stated above, the orientation of the ketone obtained from 4-*tert.*-butyltoluene was not satisfactorily determined. In the other three cases, the products were proved to be the 5-alkyl-2-methylacetophenones (VIII, IX, and X), by hypobromite oxidation to the 5-alkyl-2-methylbenzoic acids previously synthesised from intermediates of known orientation.

Experimental

(Microanalyses are by Dr.Ing. A. Schoeller, Berlin. M. p.s and b. p.s are uncorrected.)

5-tert.-*Butyl-2-methylbenzoic acid* (IV).—2-Amino-4-*tert.*-butyltoluene (12 g.) in sulphuric acid (10 ml. in 150 ml. of water) was diazotised in the normal manner, then treated with potassium iodide (25 g. in 50 ml. of water), and left at room temperature for 1 hour. The mixture was then warmed cautiously on the steam-bath until the evolution of nitrogen ceased, a little sodium hydrogen sulphite added, and the mixture steam-distilled. The distillate was extracted with ether, the extract washed (2N-sulphuric acid, water, 2N-sodium hydroxide, and water) and dried ($CaCl_2$), and the solvent removed. The residue on distlllation *in vacuo* gave 4-tert.-*butyl-2-iodotoluene* (7 g.), b. p. 148°/28 mm. (Found: I, 46·1. $C_{11}H_{15}I$ requires I, 46·35%).

2-*Bromo*-4-tert.-*butyltoluene*.—Bromine (24 g.) was cautiously added to a mixture of *p-tert.*-butyltoluene (21 g.) (Verley, *Bull. Soc. chim.*, 1898, **19**, 68) and iodine (0·25 g.) with occasional cooling. After the initial reaction had subsided, the mixture was heated on the steam-bath to expel as much hydrogen bromide as possible, and then steam-distilled. The distillate was

extracted with ether, the extract washed (water, 2N-sodium carbonate, 2N-sodium thiosulphate, and water) and dried ($CaCl_2$), the solvent removed, and the residue distilled *in vacuo*. The fraction of b. p. 115—120°/17 mm. was redistilled, giving 2-*bromo*-4-tert.-*butyltoluene* (19 g.), b. p. 117°/13 mm. (Found : Br, 35·0. $C_{11}H_{15}Br$ requires Br, 35·2%).

5-tert.-*Butyl*-2-*methylbenzoic Acid*.—Into a thoroughly dried " Sparklet " soda syphon was placed 2-bromo-4-*tert.*-butyltoluene (18 g.), magnesium ribbon (2 g.; dried at 110°), absolute ether (60 ml.), and dry ethyl bromide (two drops). A reflux condenser fitted with a calcium chloride tube was inserted into the neck of the syphon, which was then heated very cautiously (to avoid cracking) in a water-bath and kept at about 60° until the formation of the Grignard reagent was complete (about 12 hours). The syphon was then cooled in water, and next immersed in ice-water. The condenser was removed, the ordinary syphon-head (with the syphon-tube cut off) replaced, and the syphon cautiously charged with one " Sparklet " bulb of carbon dioxide. The gas was then immediately released, to remove as much air as possible, and the syphon again charged with carbon dioxide. The syphon was then left in ice-water for 2 days. The reaction mixture separated into an upper ethereal and a lower resinous layer. The pressure was then released, the syphon-head was removed, and the contents of the syphon were well shaken and poured on to a mixture of sulphuric acid (5N; 40 ml.) and ice (60 g.). After 10 minutes the ethereal layer was separated and extracted with 2N-sodium carbonate. The aqueous extract was acidified with dilute sulphuric acid. An oil separated, which rapidly solidified. This was filtered off, washed with water, and distilled in steam. The distillate was then cooled, and the acid filtered off and recrystallised from aqueous alcohol, giving 5-tert.-*butyl*-2-*methylbenzoic acid* as long white needles, m. p. 101° (6 g.) (Found : C, 75·0; H, 8·3. $C_{12}H_{16}O_2$ requires C, 75·0; H, 8·4%). An identical product was obtained when 4-*tert.*-butyl-2-iodotoluene was employed.

5-*Ethyl*-2-*methylbenzoic acid* (I) was prepared from 2-amino-4-ethyltoluene through 4-*ethyl*-2-*iodotoluene*, b. p. 116—117°/10 mm. (Found : I, 51·4. $C_9H_{11}I$ requires I, 51·6%), and its Grignard reagent. It crystallised from aqueous alcohol in long needles, m. p. 73·5° (Found : C, 73·2; H, 7·2. $C_{10}H_{12}O_2$ requires C, 73·2; H, 7·4%).

2-*Methyl*-5-n-*propylbenzoic acid* (II).—4-Methyl-3-nitropropiophenone (25 g.) was reduced with amalgamated zinc (200 g.; prepared as described by Brady and Day, *J.*, 1934, 117) and hydrochloric acid (200 ml. of concentrated acid in 200 ml. of water), a further 600 ml. of concentrated acid being added during 6 hours. After cooling, sodium hydroxide (400 g. in 600 ml. of water) was added, and the mixture distilled in steam. The distillate was extracted with ether, the extract dried (KOH), the solvent removed, and the residue distilled *in vacuo*. 2-Amino-4-*n*-propyltoluene (2 g.) was obtained as a colourless oil, b. p. 128—130°/13 mm., with an unpleasant odour. The *acetyl* derivative crystallised from aqueous alcohol as a felted mass, m. p. 127° (Found : C, 75·1; H, 9·0; N, 7·4. $C_{12}H_{17}ON$ requires C, 75·4; H, 9·0; N, 7·3%). The poor yield of the amine obtained in this preparation compares with that of 2-amino-4-ethyltoluene obtained by Brady and Day (*ibid.*, p. 120) in the reduction of 4-methyl-3-nitroacetophenone.

2-*Iodo*-4-n-*propyltoluene* was obtained from the amine in the normal manner as a colourless oil, b. p. 131—133°/14 mm. (Found : I, 48·6. $C_{10}H_{13}I$ requires I, 48·8%).

p-*n*-Propyltoluene (von Auwers, *Annalen*, 1919, **419**, 112) yielded 2-*bromo*-4-n-*propyltoluene* as a colourless oil, b. p. 105°/12 mm. (Found : Br, 37·4. $C_{10}H_{13}Br$ requires Br, 37·6%). Both 2-bromo- and 2-iodo-4-*n*-propyltoluene, on conversion into the Grignard reagent and treatment with carbon dioxide, yielded 2-*methyl*-5-n-*propylbenzoic* acid, long needles, m. p. 57° (from aqueous alcohol) (Found : C, 74·2; H, 8·0. $C_{11}H_{14}O_2$ requires C, 74·2; H, 7·9%).

Friedel–Crafts Experiments.—Method I. Acetic anhydride (69 g., 1 mol.) was run into the mechanically stirred mixture of *p-tert.*-butyltoluene (100 g., 1 mol.), carbon disulphide (200 ml.), and freshly sublimed aluminium chloride (320 g., *ca.* 3·5 mols.) during 30 minutes. The warm mixture was refluxed with stirring for a further 2 hours, and then poured on ice. The carbon disulphide layer was separated, the aqueous layer was extracted with ether, the combined carbon disulphide and ethereal extracts were washed with water and dried ($CaCl_2$). The solvent was removed, and the residue fractionally distilled at 17 mm. The fraction boiling below 110° (8 g.) consisted mainly of unchanged hydrocarbon. That of b. p. 110—120° (21 g.) was purified through its semicarbazone and yielded pure *p*-methylacetophenone (10 g.), b. p. 113°/17 mm. The semicarbazone, a white microcrystalline solid from aqueous alcohol, had m. p. 207° (unchanged on admixture with an authentic specimen) (Found : C, 62·6; H, 7·0; N, 21·9. Cal. for $C_{10}H_{13}ON_3$: C, 62·8; H, 6·9; N, 22·0%). The fraction of b. p. 120—140°/1 (7 g.) was discarded, and that distilling between 140 and 155° (43 g.) was converted into the semicarbazone which, recrystallised three times from aqueous alcohol and then hydrolysed, gave a pure tert.-

butylmethylacetophenone (21 g.), b. p. 147°/17 mm. (Found : C, 81·8; H, 9·6. $C_{13}H_{18}O$ requires C, 82·1; H, 9·55%). The *semicarbazone*, white needles from aqueous alcohol, had m. p. 197° (Found : C, 68·0; H, 8·7; N, 16·7. $C_{14}H_{21}ON_3$ requires C, 68·0; H, 8·6; N, 17·0%). The mixed m. p. with the semicarbazone of *p*-methylacetophenone was *ca.* 174°. Meissel (*Ber.*, 1899, **32**, 2422) records a b. p. of 240—245° for 2-(or 3-)acetyl-4-*tert.*-butyltoluene, whilst Lacourt (*Bull. Soc. chim. Belg.*, 1929, **38**, 16) gives b. p. 133—135°/12 mm., and the m. p. of the semicarbazone as 190°. Baur-Thurgau (*Ber.*, 1898, **31**, 1345) gives the b. p. of 4-*tert.*-butyl-2-methylacetophenone as 255—258°.

Method II. To freshly sublimed aluminium chloride (51 g., 1 mol.) and carbon disulphide (100 ml.), cooled with water, was added a mixture of *p*-ethyltoluene (46 g., 1 mol.) and acetyl chloride (30 g., 1 mol.) during *ca.* 90 minutes. Stirring was then continued at room temperature for a further 6 hours. The dark brown mixture was poured on crushed ice, and worked up as in Method I. The crude product was fractionally distilled *in vacuo* (15 mm.). The fraction boiling below 100° (4 g.) consisted of unchanged hydrocarbon. That of b. p 100—112° (1 g.) was proved to contain no *p*-methylacetophenone by means of the semicarbazone. The fraction distilling between 112 and 122° (45 g.) was crude *5-ethyl-2-methylacetophenone* (VIII). It was purified by conversion into the semicarbazone; recrystallisation three times from aqueous alcohol, hydrolysis, and redistillation gave the pure *ketone* (20 g.) as a colourless pleasant-smelling liquid, b. p. 112—113°/13 mm. (Found : C, 81·3; H, 8·6. $C_{11}H_{14}O$ requires C, 81·5; H, 8·7%). The *semicarbazone*, white needles, had m. p. 135° (Found : C, 65·9; H, 7·9; N, 19·0. $C_{12}H_{17}ON_3$ requires C, 65·8; H, 7·8; N, 19·2%).

The following ketones were prepared in a similar manner : *2-Methyl-5-n-propylacetophenone* (IX), b. p. 122°/11 mm. (Found : C, 81·9; H, 9·2. $C_{12}H_{16}O$ requires C, 81·8; H, 9·1%) [*semicarbazone*, white needles (from aqueous alcohol), m. p. 163° (Found : C, 66·8; H, 8·1; N, 18·2. $C_{13}H_{19}ON_3$ requires C, 66·95; H, 8·2; N, 18·0%)]. 2-Methyl-5-*iso*propylacetophenone (X), b. p. 125°/14 mm. (Klages and Lickroth, *Ber.*, 1899, **32**, 1563, give b. p. 142°/37 mm.; Lacourt, *Bull. Soc. chim. Belg.*, 1929, **38**, 17, gives 124—125°/12 mm.) [semicarbazone, white needles (from aqueous alcohol), m. p. 149° (Lacourt, *loc. cit.*, gives m. p. 147°) (Found : C, 66·8; H, 8·3; N, 18·0%)].

Oxidation of the Alkylmethylacetophenones.—Bromine (39·6 g., 3 mol.) was dissolved, with cooling, in cold aqueous sodium hydroxide (600 ml. of 4%) contained in a large bottle. 5-Ethyl-2-methylacetophenone (13·4 g., 1 mol.) was added, and the bottle mechanically shaken until the yellow colour of the solution had disappeared (*ca.* 30 hours). A heavy layer of bromoform separated. The liquors were washed twice with ether, the washings being discarded, the aqueous layer was acidified, and the precipitated acid extracted with ether. The ethereal solution was extracted with 2N-sodium carbonate, and the alkaline extract acidified. After filtration and washing with water, the acid was distilled in steam and finally recrystallised from aqueous alcohol, 5-ethyl-2-methylbenzoic acid (8·6 g.), m. p. 73·5°, being obtained.

Similar oxidation of 2-methyl-5-*n*-propylacetophenone yielded 2-methyl-5-*n*-propylbenzoic acid, m. p. 57°. In both cases, the carboxylic acids were identical with those prepared *via* the Grignard reagents. Hypobromite oxidation of 2-methyl-5-*iso*propylacetophenone yielded 2-methyl-5-*iso*propylbenzoic acid (III), which crystallised from aqueous alcohol in needles, m. p. 70·5° (Le Fèvre, *J.*, 1933, 983, gives m. p. 70°; Lester and Bailey, *J. Amer. Chem. Soc.*, 1946, **68**, 375, give 71°) (Found : C, 74·1; H, 8·1. Calc. for $C_{11}H_{14}O_2$: C, 74·2; H, 7·9%), identical with those obtained by carboxylation of the Grignard reagent from 2-bromo-4-*iso*propyltoluene (Le Fèvre, *loc. cit.*).

When the *tert.*-butylmethylacetophenone described above was oxidised in the same manner, a *tert.-butylmethylbenzoic acid* was obtained which crystallised from aqueous alcohol in glistening white plates, m. p. 144° (mixed m. p. with 5-*tert.*-butyl-2-methylbenzoic acid, *ca.* 70—72°) (Found : C, 74·5; H, 8·3%; equiv., 196. $C_{11}H_{15}{\cdot}CO_2H$ requires C, 75·0; H, 8·3%; equiv., 192).

Attempt to synthesise 2-tert.-*Butyl-5-methylbenzoic Acid* (V).—4-*tert.*-Butyl-2 : 6-dinitrotoluene (78 g.) was reduced with excess of granulated tin and hydrochloric acid in the normal manner. After about 20 hours' refluxing, the mixture was cooled and poured into sodium hydroxide (850 g. in 1700 ml. of water), and the whole thoroughly shaken. After cooling, the diamine was extracted with ether, the extract washed and dried (KOH), and the solvent removed, leaving crude 2 : 6-diamino-4-*tert.*-butyltoluene as an oil, which rapidly solidified to colourless crystals, darkening on storage. The crude diamine (45 g.) was boiled for 2—3 minutes with acetic anhydride (54 g., 5% excess); the product, after recrystallisation from alcohol, was 2 : 6-*diacetamido*-4-tert.-*butyltoluene*, a felted mass, m. p. 298° (61 g.) (Found : C, 68·5; H, 8·5; N, 10·8. $C_{15}H_{22}O_2N_2$ requires C, 68·7; H, 8·5; N, 10·7%).

2 : 6-*Diacetamido*-3-*bromo*-4-tert.-*butyltoluene* (VI).—2 : 6-Diacetamido-4-*tert.*-butyltoluene (46 g., 1 mol.) and glacial acetic acid (150 ml.) were warmed on the water-bath to dissolve as much of the solid as possible, then cooled to room temperature, and a solution of bromine (28·1 g., 1 mol.) in acetic acid (20 ml.) added, with shaking. The mixture was heated under reflux on the steam-bath, dissolution being complete within 10 minutes. After 1 hour, white crystals began to separate. Heating was continued until all the bromine disappeared (*ca.* 8 hours). The cooled product was then poured into water (1200 ml.), filtered off, washed with water, and recrystallised twice from alcohol. 2 : 6-*Diacetamido*-3-*bromo*-4-tert.-*butyltoluene* (31 g.) was obtained as a white, granular solid, m. p. 252° (decomp.) (Found : C, 52·9; H, 6·3; N, 7·9; Br, 23·2. $C_{15}H_{21}O_2N_2Br$ requires C, 52·8; H, 6·2; N, 8·2; Br, 23·5%.

We thank Dr. O. L. Brady for advice and one of us (E. P. T.) thanks Brighton Education Committee for the provision of facilities for this work, which was carried out during 1935—1939.

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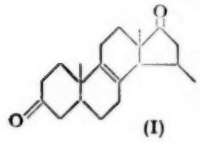
198. *Experiments bearing on the Synthesis of Cortisone. Part I.* Some* cyclo*Pentenone Derivatives.*

By R. M. ACHESON and SIR ROBERT ROBINSON.

3-Methyl*cyclo*pent-2-enone has been prepared by the cyclisation of acetonylacetone. A reconsideration of Goss and Ingold's supposed bi*cyclo*pentane derivatives (*J.*, 1928, 1268) has suggested that these are *cyclo*pentadienes or *cyclo*pentenones and the assumption of a bridged ring is unnecessary. For example, in the case of 2-methyl-4-keto*cyclo*pent-2-ene-1-carboxylic acid, the monocyclic structure is the only one consistent with the chemical and physical evidence.

ALTHOUGH the total synthesis of cortisone has already been achieved by two distinct routes [(*a*) Cardwell, Cornforth, Duff, Holtermann, and Robinson, *Chem. and Ind.*, 1951, 389; Rosenkrantz, Pataki, and Djerassi, *J. Amer. Chem. Soc.*, 1951, **73**, 4057; (*b*) Woodward, Sondheimer, and Taub, *J. Amer. Chem. Soc.*, 1951, **73**, 4057], the methods adopted have been so tortuous that these accomplishments have only an indirect value in relation to the preparation of the hormone by a feasible practical synthesis. It is therefore still necessary to investigate all possible synthetic routes in the hope that the production of cortisone may thereby be facilitated.

Little use has so far been made of the Diels–Alder reaction in the synthesis of sterol derivatives from carbocyclic intermediates which later constitute the intact D-ring. The brilliant recent work of Woodward and his collaborators (*loc. cit.*) is excluded from this category by definition, since ring D as set up in the Diels–Alder reaction was later broken and then reconstituted in a different form. Experiments so far reported include the work of Dane and her collaborators (*Annalen*, 1939, **537**, 246, and earlier papers) on the addition of 2-methyl*cyclo*pent-2-ene-1 : 5-dione to 1 : 2-dihydro-7-methoxy-4-vinylnaphthalene, and that of Nazarov and Bergel'son (*Zhur. Obschei. Chim.*, 1950, **20**, 648; *Chem. Abs.*, 1950, **44**, 8913) who showed that 2 : 4-dimethyl*cyclo*pent-2-enone reacted with Δ^1-octahydro-6-keto-9-methyl-1-vinylnaphthalene to give a compound considered to be (I), although alternative structures were not excluded and one of these appears the more probable on theoretical grounds.

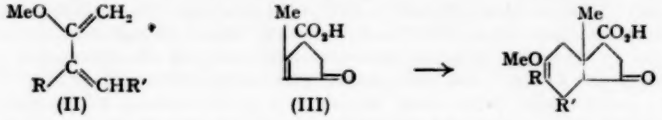


(I)

In this type of reaction it is desirable that the *cyclo*pentene derivative should be substituted in such a way that in the resulting tetracyclic molecule it will (*a*) provide the angular $C_{(13)}$-methyl group, (*b*) enable manipulation of substituents in the $C_{(17)}$-position to be carried out, and (*c*) facilitate the conversion of the *cis*-C–D-ring-junction produced in the reaction into a *trans*-linkage. The use of a substituted diene designed strongly to

* A preliminary account of an investigation in this field, which it is hoped may later be published as a Part of the present series, has already appeared (Friedmann and Robinson, *Chem. and Ind.*, 1951, 777).

orient the dienophile during the reaction is also desirable. The reaction between methoxybutadienes of type (II) and 4-keto-2-methyl*cyclo*pent-2-ene-1-carboxylic acid (III), or a

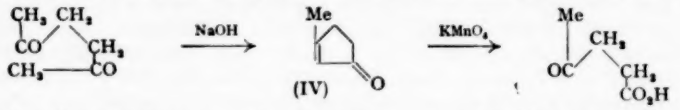


(II) (III)

derivative of the acid, which has the above desiderata for the dienophile, was therefore contemplated. As shown in the sequel it transpires that (III) is already known and we hope to use it for the purpose stated herein. It seems probable that the conjugation of the ring carbonyl group with the double bond will be paramount and will impede movement of the double bond towards the carboxyl (or ester) group. An example of the expected reaction is indicated in the formula below, given as a product from (III).

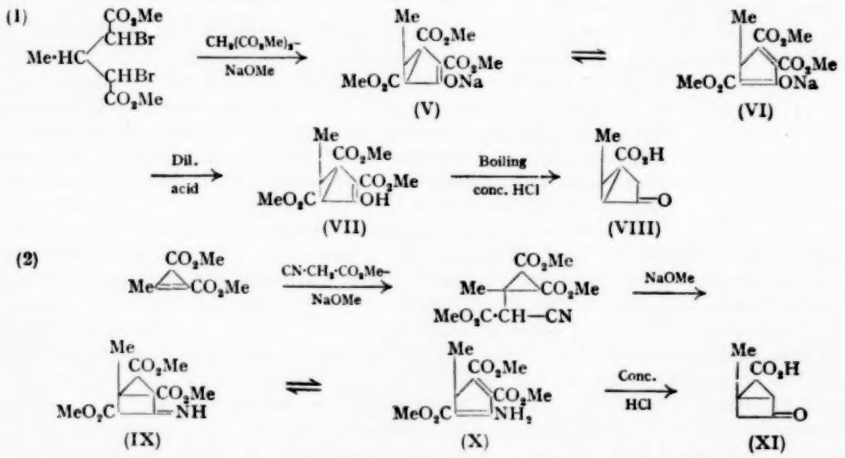
A preliminary investigation of the reaction between 3-methyl*cyclo*pent-2-enone and 2-methoxybutadiene will be reported in a subsequent communication.

Experiments were first directed towards the synthesis of 3-methyl*cyclo*pent-2-enone (IV) and it was found that this compound could be prepared from acetonylacetone by boiling 1% aqueous sodium hydroxide. The conditions for this reaction are critical. Too little alkali gives a mixture of acetonylacetone and the *cyclo*pentenone which is difficult to separate, whereas prolonged boiling or too much alkali increases the production of tar. Blaise (*Compt. rend.*, 1914, **158**, 708) has stated that it is impossible to isolate any of the *cyclo*pentenone from this reaction, the product being a red resin, but the conditions he employed were probably too drastic. Similar cyclisations of unsymmetrical diketones, in which the carbonyl groups may react with either a CH_3 or a CH_2 group and appear to favour the latter course, have been reported by Hunsdiecker (U.S.P. 2 387 587; *Chem. Abs.*, 1946, **40**, 3131). The ketone (IV) was characterised as the oxime, semicarbazone,



(IV)

and 2 : 4-dinitrophenylhydrazone. Its structure was confirmed by oxidation to lævulic acid, isolated as the 2 : 4-dinitrophenylhydrazone.



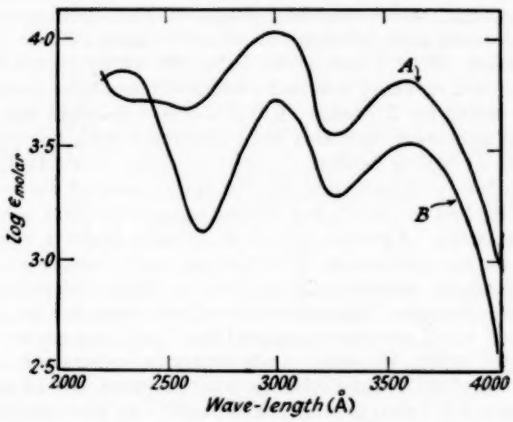
(V) (VI) (VII) (VIII) (IX) (X) (XI)

Godchot and Taboury (*Compt. rend.*, 1913, **156**, 1780) have reported the preparation of (IV) from 3-methyl*cyclo*pentanone by chlorination to 2-chloro-3-methyl*cyclo*pentanone followed by removal of hydrogen chloride. No analytical data were given, either for their

ketone, the structure of which appeared to be supported by degradation experiments, or for its oxime, m. p. 127°, or semicarbazone, m. p. 230°. As the melting points of these derivatives do not agree with those reported here, and as the refractive index of authentic 3-methyl*cyclo*pent-2-enone (n_D^{20} 1·4893) is much higher than that of Godchot and Taboury's ketone (n_D^{26} 1·4714) it is probable that the latter material was a mixture, one constituent of which may have been 3-methyl*cyclo*pentanone.

4-Keto-2-methyl*cyclo*pent-2-ene-1-carboxylic acid (III) was first prepared by Goss and Ingold (*J.*, 1928, 1268) although they failed to recognise, or at least to emphasise, its correct structure. It was obtained from two series of reactions, outlined on p. 1128 in the original formulation. Goss and Ingold found that the end products of both series of reactions, although formulated as (VIII) and (XI) respectively, were identical. Nevertheless the compound in question appears to be neither (VIII) nor (XI), but 4-keto-2-methyl-*cyclo*pent-2-ene-1-carboxylic acid (III). The *cyclo*pentenone structure for this compound was certainly mentioned as an alternative in parentheses in the experimental section of Goss and Ingold's paper, but the possibility that most of the compounds were in fact *cyclo*pentenone derivatives was kept in the background and attention was focused on the bicyclic structure. The reported oxidation of (IX or X) with hydrogen peroxide in the presence of ferrous sulphate to α- and β-methylglutaconic acids and β-acetylacrylic acid can be explained on the *cyclo*pentadieneamine formulation (X) but a *cyclo*propane derivative might well have arisen from the oxidation of (IX).

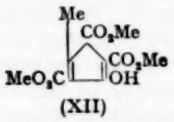
Methyl αα′-dibromo-β-methylglutarate was found to react with methyl malonate in the presence of sodium methoxide as described by Goss and Ingold, to give the sodium salt of methyl 3-hydroxy-5-methyl*cyclo*pentadiene-1 : 2 : 4-tricarboxylate (sodium salt of XII or XIII). The free hydroxy-compound, prepared from the salt with cold dilute mineral acid, distilled to give a pale yellow oil. Its absorption spectrum in methanol and that of



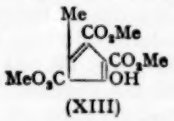
A, The sodium salt of (XII) *and/or* (XIII) *in water.*

B, Methyl 3-hydroxy-5-methylcyclopentadiene-1 : 2 : 4-tricarboxylate (XII *and/or* XIII) *in methanol.*

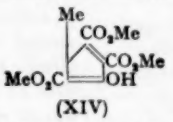
the aqueous sodium salt indicate conjugation of a high order resembling that of an aromatic system (cf. Fig.). This does not support structures (VII) and (V), which are unlikely in any case on stereochemical grounds, for these compounds. The similarity of two curves also indicates that the free acid consists largely of the hydroxy-compound (XII and/or XIII).



(XII)



(XIII)



(XIV)

This is also in accord with the immediate deep blue coloration with ferric chloride, the non-formation of ketonic derivatives, and the vigorous reaction with aqueous potassium hydrogen carbonate. The infra-red absorption of the hydroxy-compound indicates the

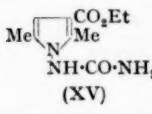
presence of a small amount of an αβ-unsaturated carbonyl group in a five-membered ring, with a large proportion of an unconjugated ester group. This suggests that the substance contains only small amounts of ketonic tautomers (in agreement with the ultra-violet absorption measurements) and of structure (XIV); the larger proportion of the material therefore consists of (XII) and/or (XIII).

Decomposition of the sodium salt with concentrated hydrochloric acid gave 4-keto-2-methyl*cyclo*pent-2-ene-1-carboxylic acid (III) characterised as the 2 : 4-dinitrophenylhydrazone. The ethyl ester was prepared from the acid with ethanolic hydrogen chloride and characterised as the semicarbazone and 2 : 4-dinitrophenylhydrazone.

An attempt to make the semicarbazone of the acid in hot aqueous solution caused decarboxylation, and 3-methyl*cyclo*pent-2-enone semicarbazone was isolated from the reaction. Decarboxylation of the acid to the free ketone, identified by its physical constants and conversion into its 2 : 4-dinitrophenylhydrazone, was also effected by hot alcoholic potassium hydroxide (cf. Stork and Burgstahler, *J. Amer. Chem. Soc.*, 1951, **73**, 3544). These experiments show conclusively that the acid has a *cyclo*pentenone structure. As the compound gives no colour with ferric chloride and is so stable to acid, the carboxyl group, considered as a substituent into the methyl*cyclo*pentenone, is unlikely to be present at position 2 or 5, and is therefore probably at position 4. This is supported by the infra-red absorption spectra of the acid and the ethyl ester, which are not consistent with any other structure. The infra-red absorption of the latter ester is also very similar to that of Hagemann's ethyl 4-keto-2-methyl*cyclo*hex-2-ene-1-carboxylate (*Ber.*, 1893, **26**, 879; cf. Schwenk and Bloch, *J. Amer. Chem. Soc.*, 1942, **64**, 3050), which was examined for comparison (Experimental section). The ultra-violet absorption of the *cyclo*pentanonecarboxylic ester in methanol showed $\lambda_{max.}$ 2300 (ε 12 150) and this confirms the *cyclo*-2-enone structure. It is very similar to the spectrum of Hagemann's ester in methanol ($\lambda_{max.}$ 2300; ε 12 900).

Various attempts were made to synthesise 4-keto-2-methyl*cyclo*pent-2-ene-1-carboxylic acid or ester from ethyl α-acetyl-lævulate, which was best prepared from bromoacetone and ethyl sodio-acetoacetate by Stevenson and Johnson's method (*J. Amer. Chem. Soc.*, 1937, **59**, 2525). Goldberg and Muller (*Helv. Chim. Acta*, 1938, **21**, 1699) report that ethyl α-acetyl-β-methyl-lævulate cyclised to ethyl 4-keto-2 : 5-dimethyl*cyclo*pent-2-ene-1-carboxylate when kept with warm water for 3 weeks. Ethyl α-acetyl-lævulate was recovered largely unchanged from this operation, and also from treatment with hot piperidine acetate, piperidine and pyridine in boiling benzene, or with ethereal *N*-ethylanilinomagnesium bromide which was apparently decomposed by the enolic form of the ester. Cold aqueous calcium chloride likewise had no effect, but boiling aqueous sodium acetate caused slow hydrolysis to acetonylacetone. Aqueous sodium hydroxide under a variety of conditions, including those used for the cyclisation of acetonylacetone, merely caused hydrolysis to the latter compound which subsequently cyclised to 3-methyl*cyclo*pent-2-enone if the conditions were vigorous enough. Hot ethanolic sodium ethoxide also gave some acetonylacetone as well as much ethyl lævulate produced by "acid hydrolysis" of the β-keto-ester (cf. Hunsdiecker, *Ber.*, 1942, **75**, 455). Cold ethanolic sodium ethoxide however gave an excellent yield of ethyl 2 : 5-dimethylfuran-3-carboxylate, the identity of which was confirmed by hydrolysis to the crystalline carboxylic acid. In this connexion it is of interest that Willstätter and Clarke (*Ber.*, 1914, **47**, 291) found that in the reaction of methyl iodide and sodium ethoxide with ethyl α-acetyl-lævulate there were indications of some cyclisation to a *cyclo*pentenone derivative.

Ethyl α-acetyl-lævulate is reported by Borsche and Spannagel (*Annalen*, 1903, **331**, 315) to react with semicarbazide to give a colourless solid, which they considered to be a pyridiazine. The ultra-violet absorption spectrum of this compound is stated to be inconsistent with this formulation by Korschun and Roll (*Bull. Soc. chim.*, 1923, [iv], **33**, 59) who suggested that the compound was (XV). They did not mention that it might also be the isomeric 4- or 5-carbethoxy-derivative of 3-methyl*cyclo*pent-2-enone semicarbazones. The latter structures have now been excluded. The compound is not identical with the semicarbazone of ethyl 4-keto-2-methyl*cyclo*pent-2-ene-1-carboxylate. It was not decomposed by pyruvic acid in boiling aqueous acetic acid and did not give any



(XV)

indication of the formation of 3-methyl*cyclo*pent-2-enone or of 2-methylbut-1-ene-1 : 4-dicarboxylic acid on decomposition with hot concentrated hydrochloric acid. The pyrrole structure (XV) is supported by the observations that the compound gives a red Ehrlich reaction, has an infra-red absorption spectrum very similar to that of ethyl 2 : 5-dimethylfuran-3-carboxylate in the 11—12-μ region, and gives a *C*-methyl value in the Kuhn–Roth determination which suggests the presence of more than two *C*-methyl groups in the molecule.

Experimental

3-Methylcyclopent-2-enone (IV).—Acetonylacetone (120 g.) was rapidly added to a boiling solution of sodium hydroxide (10 g.) in water (1 l.). After refluxing for 15 minutes the dark brown solution was quickly cooled to room temperature, saturated with salt, and extracted three times with ether (500, 250, and 250 c.c.). The extracts were washed with water (3 × 15 c.c.), dried, and evaporated. On distillation the residual dark brown oil gave the ketone (42·4 g., 42%) as a colourless liquid, b. p. 74—76°/16 mm., n_D^{20} 1·4818. The ketone could not be obtained analytically pure by repeated distillation but was purified *via* the oxime or semicarbazone, both of which were decomposed by pyruvic acid in aqueous acetic acid under the conditions of Hershberg (*J. Org. Chem.*, 1948, **13**, 542). The *ketone* thus obtained had b. p. 74°/15 mm., n_D^{20} 1·4893, and $\lambda_{max.}$ 2250 (ε 18 150) in methanol (Found : C, 74·4; H, 8·2; *C*-Me, 12·6. C_6H_8O requires C, 75·0; H, 8·3; *C*-Me, 15·6%). It is miscible with water. The *oxime* crystallised from ethanol–water (2 : 3 by volume) in colourless prisms, m. p. 144° (Found : C, 65·1; H, 8·0; N, 12·4. C_6H_9ON requires C, 64·9; H, 8·1; N, 12·6%). The m. p. of the 2 : 4-*dinitrophenylhydrazone*, m. p. 180—181° (Found : N, 20·0. $C_{12}H_{12}O_4N_4$ requires N, 20·3%), and semicarbazone, m. p. 220—221°, were unchanged by the addition of authentic samples prepared from ethyl α-acetyl-lævulate.

Oxidation. The ketone (0·24 g.) was added to a cold solution of potassium permanganate (0·83 g.) in water (23 c.c.), causing a vigorous reaction. The mixture was strongly cooled and after the addition of excess of permanganate was clarified by sulphur dioxide. The excess of sulphur dioxide was removed on a stream of air, and the solution treated with a hot solution of 2 : 4-dinitrophenylhydrazine (0·5 g.) in 2N-sulphuric acid (70 c.c.). A yellow precipitate 0·57 g., 77%) of lævulic acid 2 : 4-dinitrophenylhydrazone immediately formed. After one crystallisation from methanol it had m. p. 203—204°, alone or mixed with an authentic specimen.

Methyl 3-Hydroxy-5-methylcyclopentadiene-1 : 2 : 4-tricarboxylate (XII or XIII).—The sodium salt of this compound was prepared according to Goss and Ingold (*loc. cit.*) and crystallised from methanol in pale yellow needles m. p. 265° (decomp.) (Found : Na, 7·85. Calc. for $C_{12}H_{13}O_7Na$: Na 7·9%). On treatment with cold dilute sulphuric acid this salt gave the free hydroxy-ester (XII or XIII) which was collected with ether and distilled as a pale yellow oil, b. p. 175—180°/2 mm., n_D^{17} 1·4892 (Found : C, 53·7; H, 5·5; OMe, 33·2; *C*-Me, 4·7%; *M*, cryoscopic in camphor, 206. Calc. for $C_{12}H_{14}O_7$: C, 53·3; H, 5·2; 3OMe, 34·4; *C*-Me, 5·6%; *M*, 270). The infra-red absorption spectrum (film) showed maxima at 2·75 (OH), 2·89 (OH), 5·75 (unconjugated CO_2Me), 5·79 (conjugated CO_2Me), and 6·12 μ (conjugated C=C). There was a shoulder in the curve at 5·94 μ indicating the presence of a small amount of an αβ-unsaturated five-membered-ring carbonyl compound.

4-Keto-2-methylcyclopent-2-ene-1-carboxylic Acid (III).—The sodium derivative of methyl 3-hydroxy-5-methyl*cyclo*pentadiene-1 : 2 : 4-tricarboxylate (17·2 g.) was refluxed with concentrated hydrochloric acid (85 c.c.; *d* 1·16) for 1 hour. Much carbon dioxide was evolved and, after cooling, the brown solution was repeatedly extracted with ether (8 × 50 c.c.). The extracts were washed with saturated aqueous sodium chloride and dried. On evaporation the acid was obtained as a pale brown crystalline mass (4·6 g., 49%). The *monohydrate* separated from ether or light petroleum (b. p. 100—120°) in almost colourless needles, m. p. 60° (Found : C, 53·6; H, 6·3; *C*-Me, 6·9%; equiv., 160. $C_7H_8O_3,H_2O$ requires C, 53·2; H, 6·3; *C*-Me, 9·5%; equiv., 158). Goss and Ingold (*loc. cit.*) report m. p. 60° and analytical data for the anhydrous acid, but complete dehydration of our monohydrate was not effected by drying at 56° *in vacuo* over phosphoric anhydride. The infra-red absorption spectrum showed maxima at 2·86 (OH), 2·94 (OH), 3·88 (bonded OH), 5·85 (conjugated CO_2H), 5·95 (αβ-unsaturated five-membered-ring carbonyl) and 6·19 μ (conjugated C=C). The 2 : 4-*dinitrophenylhydrazone*, which was soluble in aqueous potassium hydrogen carbonate, was prepared from the acid and a cold solution of the reagent. It separated from dioxan in very dark yellow prisms, m. p. 227—229° (decomp., with darkening *ca.* 215°) (Found : C, 49·1; H, 3·4. $C_{13}H_{12}O_8N_4$ requires C, 48·7; H, 3·7%).

Ethyl ester. A refluxing solution of the acid (III) (0·5 g.) in dry ethanol (20 c.c.) was saturated with hydrogen chloride. Boiling was continued for 3·5 hours after which most of the solvent was removed *in vacuo*. The residual oil was treated with excess of aqueous potassium hydrogen carbonate (20%) and the *ester* collected with ether. It was a pale yellow oil (0·35 g., 66%), b. p. 127—130° (bath-temp.)/1 mm., n_D^{18} 1·4952 (Found: C, 64·1; H, 7·2. $C_9H_{12}O_3$ requires C, 64·2; H, 7·1%). It was soluble in water and gave no colour with ferric chloride. The infra-red absorption spectrum (film) showed maxima at 2·78 (OH), 2·83 (OH), 5·74 (unconjugated CO_2Et), 5·83 (αβ-unsaturated five-membered-ring ketone and at 6·13 μ (conjugated C=C). There was no band between 10·2 and 10·5 μ. The infra-red absorption spectrum (film) of Hagemann's ester was very similar and showed maxima at 2·90 (OH), 3·00 (OH), 5·77 (unconjugated CO_2Et), 5·97 (αβ-unsaturated six-membered-ring ketone), and 6·12 (conjugated C=C). We are obliged to Mr. C. A. Finch for a specimen of Hagemann's ester. The *semicarbazone* crystallised from water containing a little ethanol in colourless prisms, m. p. 220° (decomp.) (Found: C, 53·7; H, 6·7; N, 18·7. $C_{10}H_{15}O_3N_3$ requires C, 53·3; H, 6·7; N, 18·7%). The 2 : 4-*dinitrophenylhydrazone* separated from ethyl acetate in orange red needles, m. p. 186° (Found: C, 51·5; H, 4·6; N, 15·8. $C_{15}H_{16}O_6N_4$ requires C, 51·7; H, 4·6; N, 16·1%).

Decarboxylation. (i) A solution of the acid (0·5 g.) and potassium hydroxide (0·4 g.) in ethanol (10 c.c.) was refluxed for 17 hours. Most of the ethanol was then removed *in vacuo* and the residual liquid diluted with water. After saturation with salt the mixture was repeatedly extracted with ether. Distillation of the dried extract gave 3-methyl*cyclo*pent-2-enone as a colourless oil, b. p. 74—80° (bath-temp.)/16 mm., n_D^{20} 1·4884. It was characterised as the 2 : 4-dinitrophenylhydrazone which after one crystallisation from *n*-propanol had m. p. 181° unchanged by the addition of an authentic specimen (Found: C, 51·8; H, 4·3; N, 20·4%).

(ii) Carbon dioxide was evolved when an attempt was made to convert the keto*cyclo*pentenecarboxylic acid into its semicarbazone with hot aqueous sodium acetate and semicarbazide hydrochloride. After the mixture had cooled the white precipitate of 3-methyl*cyclo*pent-2-enone semicarbazone was collected. It did not react with aqueous potassium hydrogen carbonate and crystallised from ethanol in almost colourless plates, m. p. 217° alone or mixed with an authentic specimen (Found: C, 55·0; H, 7·0%).

The Hydrolysis and Cyclisation Reactions of Ethyl α-Acetyl-lævulate.—(i) *With sodium acetate.* The ester (15·0 g.) was refluxed with a solution of sodium acetate (20 g.) in water (100 c.c.) for 16 hours. After cooling, the solution was repeatedly extracted with ether, the extracts being washed with brine and dried. No keto*cyclo*pentenecarboxylic acid could be isolated from the aqueous layer. On distillation the ethereal solution gave acetonylacetone (5·25 g., 57%), b. p. 77—85°/14 mm., identified as the bis-2 : 4-dinitrophenylhydrazone, m. p. 258° (decomp.), and unchanged ester (2·8 g., 19%), b. p. 128—130°/14 mm.

(ii) *With semicarbazide.* A white precipitate of ethyl 2 : 5-dimethyl-1-ureidopyrrole-3-carboxylate was immediately formed when ethyl α-acetyl-lævulate (10·0 g.) was added to a hot solution of semicarbazide hydrochloride (12·0 g.) and sodium acetate (9·0 g.) in water (100 c.c.). After 20 minutes on a steam-bath the mixture was cooled and the pyrrole (10·3 g., 85%) collected, washed with water, and dried. It crystallised from aqueous ethanol in colourless needles, m. p. 229—230° (Found: C, 53·5; H, 6·8; N, 18·5; OEt, 21·8; *C*-Me, 14·0. Calc. for $C_{10}H_{15}O_2N_3$: C, 53·3; H, 6·7; N, 18·7; OEt, 20·0; 3*C*-Me, 20·0%). Borsche and Spannagel (*loc. cit.*) give m. p. 230°. An unstable crystalline modification, m. p. 220°, occasionally separated in short, colourless prisms from the same solvent (Found: C, 53·1; H, 6·8; N, 18·6; OEt, 19·3%); it had the same infra-red spectrum as the higher-melting material, and a mixture of the two melted sharply at 228°. Admixture with ethyl 4-keto-2-methyl*cyclo*pent-2-ene-1-carboxylate semicarbazone depressed the m. p. to 195—200°.

(iii) *With aqueous sodium hydroxide.* (*a*) The ester (5·0 g.) was refluxed with a solution of sodium hydroxide (2·0 g.) in water (50 c.c.) for 12 hours. After cooling, the solution was repeatedly extracted with ether. No acidic material could be isolated from the aqueous layer. The ethereal extracts were washed with water, dried, and distilled, giving 3-methyl*cyclo*pent-2-enone (0·7 g., 27%) as a colourless oil, b. p. 83—85° (bath-temp.)/18 mm., n_D^{20} 1·4878. The 2 : 4-dinitrophenylhydrazone separated from ethyl acetate or *n*-propanol in orange-red needles, m. p. 181° (Found: C, 52·4; H, 4·3; N, 20·1. $C_{12}H_{12}O_4N_4$ requires C, 52·2; H, 4·3; N, 20·3%). The *semicarbazone* separated from ethanol in colourless plates, m. p. 220—221° (Found: C, 54·9; H, 6·9. $C_7H_{11}ON_3$ requires C, 54·9; H, 7·2%).

(*b*) The ester (10·0 g.) was added to a boiling solution of sodium hydroxide (1·0 g.) in water (100 c.c.) and refluxing was continued for 15 minutes. The solution was rapidly cooled, acidified (much carbon dioxide was evolved), and rapidly extracted with ether. No acidic material

could be isolated from the aqueous layer. The ether contained unchanged ester (2·0 g., 20%), and acetonylacetone (2·76 g., 45%) identified as the bis-2 : 4-dinitrophenylhydrazone m. p. 256—258° (decomp.) alone or mixed with an authentic specimen.

(*c*) The ester (10·0 g.) was added to a cold solution of sodium hydroxide (4·4 g.) in water (100 c.c.). After 14 hours the solution was acidified and extracted with ether. Distillation of the extract gave a colourless liquid, b. p. 72—80°/15 mm., n_D^{18} 1·4620, which contained *ca.* 60% of 3-methyl*cyclo*pent-2-enone and *ca.* 40% of acetonylacetone estimated as their derivatives with 2 : 4-dinitrophenylhydrazine.

(iv) *With sodium ethoxide.* (*a*) The ester was recovered unchanged after being kept in a cold solution of sodium ethoxide (0·5% of sodium) in absolute ethanol for 72 hours.

(*b*) The ester (10·0 g.) was added to a cold solution of sodium (1·35 g.) in absolute ethanol (200 c.c.). After 18 hours at room temperature the solution was accurately neutralised with concentrated hydrochloric acid (6·0 c.c.; *d* 1·16), sodium chloride being precipitated. Anhydrous magnesium sulphate was then added, and after a short time the mixture was filtered. Distillation of the filtrate gave ethyl 2 : 5-dimethylfuran-3-carboxylate as a colourless oil (7·5 g., 83%), b. p. 90—94°/15 mm., n_D^{23} 1·4693. On hydrolysis with alcoholic potassium hydroxide this ester gave a quantitative yield of 2 : 5-dimethylfuran-3-carboxylic acid, which separated from light petroleum (b. p. 80—100°) in colourless prisms, m. p. 135° (Found : C, 60·3; H, 5·7. Calc. for $C_7H_8O_3$: C, 60·0; H, 5·7%). Scott and Johnson (*J. Amer. Chem. Soc.*, 1932, **54**, 2549) give b. p. 99—101°/14 mm. and n_D^{20} 1·46897 for the ester, and m. p. 135° for the furancarboxylic acid.

(*c*) The ester (10·0 g.) was refluxed with a solution of sodium (0·5 g.) in dry ethanol (100 c.c.) for 2 hours. After cooling, the solution was accurately neutralised with concentrated hydrochloric acid (1·3 c.c.; *d* 1·16), dried, and evaporated. The residual brown oil was dissolved in ether, the solution was extracted with 5% aqueous sodium hydroxide, and the extracts were retained. On distillation the dried ethereal solution gave ethyl lævulate (2·7 g., 35%) as a colourless oil, b. p. 101—102°/22 mm., n_D^{20} 1·4238 (Found : C, 58·4; H, 8·6. Calc. for $C_7H_{12}O_3$: C, 58·3; H, 8·3%). The 2 : 4-dinitrophenylhydrazone separated from methanol in yellow prisms, m. p. 107° (Found : C, 48·4; H, 5·0; N, 17·6. Calc. for $C_{13}H_{16}O_6N_4$: C, 48·1; H, 4·9; N, 17·3%). Auwers (*Ber.*, 1911, **44**, 3533) gives b. p. 95°/15 mm. and n_D^{16} 1·4242 for the ester. Cowley and Schuette (*J. Amer. Chem. Soc.*, 1933, **55**, 3644) report m. p. 101° for the 2 : 4-dinitrophenylhydrazone. The aqueous sodium hydroxide was acidified and extracted repeatedly with ether. Evaporation of the dried extract gave a brown oil (1·2 g.) from which only acetonylacetone, identified as the bis-2 : 4-dinitrophenylhydrazone, m. p. 258° (decomp.) alone or mixed with an authentic specimen, and ethyl α-acetyl-lævulate, identified as ethyl 2 : 5-dimethyl-1-ureidopyrrole-3-carboxylate, m. p. 228° (Found : C, 53·4; H, 6·5; N, 18·7%), could be isolated.

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Dyson Perrins Laboratory, Oxford University. [*Received, November 29th*, 1951.]

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199. *The Replacement of Secondary Tosyloxy-groups by Iodine in Polyhydroxy-compounds.*

By N. K. Matheson and S. J. Angyal.

The replacement of secondary tosyloxy-groups by iodine in open-chain polyhydroxy-derivatives has been studied. It has been found that reaction occurs under conditions comparable with those necessary to replace many primary toxyloxy-groups. The ease of the reaction is dependent on steric factors and is greatly diminished when the tosyl group is attached to a carbon atom which is a member of a ring.

It is generally accepted that secondary tosyloxy-groups in polyhydroxy-compounds (carbohydrates) are not replaced by iodine when the compounds are heated with sodium iodide in acetone under certain standard conditions, while primary tosyloxy-groups react

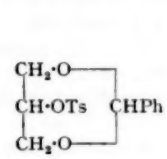
readily. Oldham and Rutherford, who first formulated this rule (*J. Amer. Chem. Soc.*, 1932, **54**, 366), have found that in aldohexoses only the tosyloxy-group attached to the terminal carbon atom was exchanged on 2 hours' heating at 100°, and that this exchange was quantitative. Other authors have extended this work to aldopentoses (Levene and Raymond, *J. Biol. Chem.*, 1933, **102**, 317), ketoses (Gardner and Lee, *J. Org. Chem.*, 1947, **12**, 733), and polyhydric alcohols (Hann, Ness, and Hudson, *J. Amer. Chem. Soc.*, 1944, **66**, 73), reaching the same conclusion. There are many examples in the work of Hudson and his co-workers of replacement of primary, but none of secondary, groups. Thus 1 : 3-4 : 6-dimethylene 2 : 5-ditosyl dulcitol and the corresponding dibenzylidene derivative were unchanged after being heated with sodium iodide in acetic anhydride (*ibid.*, 1942, **64**, 986). A 1 : 3-4 : 6- or 1 : 3-5 : 6-dimethylene ditosyl D-mannitol, heated in acetone at 100° or in acetic anhydride at 140°, did not react (*idem, ibid.*, 1943, **65**, 67). 1 : 3-4 : 6-Dimethylene 2 : 5-ditosyl D-talitol was unchanged after being heated for 48 hours at 80° in acetonylacetone (*idem, ibid.*, 1947, **69**, 624). These considerations, however, apply only to isolated tosyl groups; it is well-known that a secondary tosyl group adjacent to a primary tosyl group is reactive (*e.g.*, Bladon and Owen, *J.*, 1950, 598; Tipson and Cretcher, *J. Org. Chem.*, 1943, **8**, 95).

Subsequent work has shown that to replace some primary tosyloxy-groups more vigorous conditions are required than those specified by Oldham and Rutherford (*loc. cit.*). Foster, Overend, Stacey, and Wiggins (*J.*, 1949, 2542) found that some derivatives of 6-tosyl galactose needed much longer heating. Seeback, Sorkin, and Reichstein (*Helv. Chim. Acta*, 1945, **28**, 934) report that methyl 2 : 3-4 : 5-dibenzylidene 6-tosyl D-idonate did not react with sodium iodide on being heated for 5 hours at 100°. The reaction is particularly slow with ketoses in which the tosyl group is adjacent to the glycosidic carbon atom (Gardner and Lee, *loc. cit.*); in one case, that of 2 : 3-4 : 5-di*iso*propylidene 1-tosyl fructose, no reaction occurred on heating at 130° for 3 days (Müller and Reichstein, *Helv. Chim. Acta*, 1938, **21**, 263; Levene and Tipson, *J. Biol. Chem.*, 1937, **120**, 607).

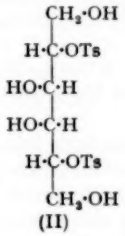
Secondary tosyloxy-groups are, as a rule, unreactive even under these more vigorous conditions; but several exceptions have been reported. Oldham and Rutherford (*loc. cit.*) have already given warning that prolonged heating may cause gradual exchange of secondary groups. Failure of an attempt to determine quantitatively the primary and secondary tosyloxy-groups in cellulose by the iodine exchange reaction (Malm, Tanghe, and Laird, *J. Amer. Chem. Soc.*, 1948, **70**, 2740) was traced to the slow reaction of the secondary groups. In 2 : 5-ditosyl 1 : 4-3 : 6-dianhydro-D-mannitol both tosyloxy-groups were replaced on 3 hours' heating at 120° (Hockett, Fletcher, Sheffield, Goepp, and Soltzberg, *J. Amer. Chem. Soc.*, 1946, **68**, 930) and in the corresponding D-sorbitol derivative one tosyloxy-group was exchanged under similar conditions (*idem, ibid.*, p. 927). Helferich and Gnüchtel (*Ber.*, 1938, **71**, 712) found that 1 : 2 : 3 : 6-tetra-acetyl 4-methanesulphonyl β-D-glucose, after 70 hours at 135°, gave the calculated amount of sodium methanesulphonate, and the iodo-compound could be isolated in good yield. Helferich assumed that methanesulphonyl groups react faster than tosyl groups; but this explanation was rendered invalid by the work of Foster *et al.* (*loc. cit.*) who found methanesulphonyl not more but rather somewhat less reactive. Curiously, the reaction of sodium iodide with 1 : 2 : 3 : 6-tetra-acetyl 4-tosyl D-glucose, the tosyl analogue of Helferich's methanesulphonyl compound, has not yet been reported.

In spite of these exceptions, the reaction with sodium iodide is still widely used as a diagnostic aid in locating tosyl groups (*e.g.*, Foster, Overend, and Stacey, *J.*, 1951, 976, 982; Foster and Overend, *J.*, 1951, 1132). Nevertheless, it is known that secondary tosyloxy-groups attached to simple hydroxy-compounds react readily; *e.g.*, 1-propyl-*n*-butyl toluene-*p*-sulphonate is converted into the iodide at room temperature (Tipson, Clapp, and Cretcher, *J. Org. Chem.*, 1947, **12**, 133). It occurred to us that most of the unreactive secondary tosyloxy-groups were attached to carbon atoms which were members of a ring (either a pyranose or furanose, or an acetal ring); primary tosyloxy-groups, naturally, could not be thus located. In order to see whether this difference is an important factor we tested a number of compounds containing secondary tosyloxy-groups which were not attached to rings.

As the simplest case of a secondary tosyloxy-group attached to a polyhydric alcohol, the synthesis of glycerol 2-toluene-*p*-sulphonate was undertaken. 5-Hydroxy-2-phenyl-1 : 3-dioxan was treated with toluene-*p*-sulphonyl chloride, and the resulting ring-compound (I) was found to react so readily with sodium iodide that it was not thought necessary to try the unsubstituted glycerol 2-toluene-*p*-sulphonate. A number of hexitols partly esterified with toluene-*p*-sulphonic acid (II—VIII) were then prepared, varying in con-



(I)



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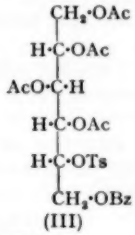

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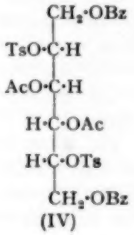
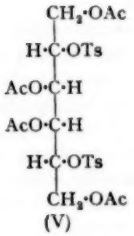


(IV)

(Ts = *p*-$C_6H_4Me{\cdot}SO_2$–).



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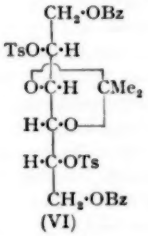

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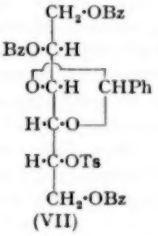

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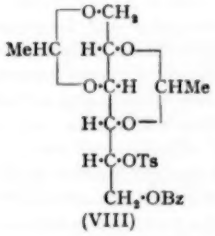

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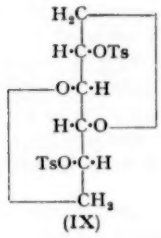

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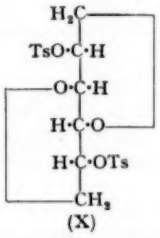
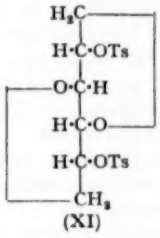


(X)



(XI)

Replacement of tosyloxy-groups in hexitols

Compound	Yield (%) of sodium toluene-*p*-sulphonate * (1)	(2)	(3)	Compound	Yield (%) of sodium toluene-*p*-sulphonate * (1)	(2)	(3)
(I)	>100%	—	—	(VI) §	11	54	—
(II) §	88	—	—	(VII)	9	—	95
(III)	57	—	—	(VIII)	0	82	100
(IV) §	45	>100%	—	(IX)	0	0	33
(V) §	0	57	>100%				

* Conditions : (1) 2 hours at 100—103°; (2) 3 hours at 115—120°; (3) 4 hours at 135—140°.
§ Yield calc. on replacement of both tosyloxy-groups.

figuration and in substituents; they were heated with sodium iodide in acetone, and the precipitated sodium toluene-*p*-sulphonate was collected and weighed. The results are given in the Table.

It is evident from these results that some secondary tosyloxy-groups in hexitols are replaced by iodine under conditions such that primary tosyloxy-groups are not readily replaced in some hexitol and hexose derivatives. Thus 2 : 4-3 : 5-dimethylene [1]1 : 6-ditosyl iditol gave only a 10% yield on 2 hours' heating at 100° (Hann and Hudson, *J. Amer. Chem. Soc.*, 1945, **67**, 602); and 3 : 4-*iso*propylidene 2 : 6-ditosyl methyl-D-galactos-

ide gave a 17·9% yield of sodium toluene-*p*-sulphonate after 5 hours at 115—125° (Foster *et al.*, *loc. cit.*). In contrast to this, 2 : 5-ditosyl dulcitol (II), as shown in the Table, gave a high yield in 2 hours at 100°.

It is apparent that factors other than the primary or secondary nature of the tosyloxy-group have a profound influence on the reaction rate. Of these factors the following—which are all steric—can be mentioned:

(1) The nature of adjacent groups. The reactivity of a secondary tosyloxy-group in hexitols diminishes in the following order: tosyl next to free hydroxyl, tosyl next to an ester group, tosyl next to an acetal ring (compare II and V, III and VIII). The reactivity of primary tosyloxy-groups is similarly affected (cf. Foster *et al.*, *loc. cit.*).

(2) Configurational differences exert an effect (compare III, IV, and V) which is not understood.

(3) The most important retarding factor is the attachment of the tosyloxy-group to a carbon atom which is in a ring, particularly in a six-membered ring. This is the same effect that causes *cyclo*pentyl halides to react slower, and *cyclo*hexyl halides even more slowly, than aliphatic halogen compounds. (For a discussion and references see Brown, Fletcher, and Johannesen, *J. Amer. Chem. Soc.*, 1951, **73**, 212, with whose conclusions, however, we do not concur.) A simple example, in the case of tosyl groups, is the comparison between 1-*n*-propyl-*n*-butyl toluene-*p*-sulphonate—which gave a 24% yield of sodium toluene-*p*-sulphonate on being kept for 2 hours with a solution of sodium iodide in acetone—and *cyclo*hexyl toluene-*p*-sulphonate which gave only a 3% yield under the same conditions (Tipson, Clapp, and Cretcher, *loc. cit.*). In a six-membered ring with few substituents the reaction will still be sufficiently fast at 100°: toluene-*p*-sulphonates of the *cyclo*hexanediols react (Clarke and Owen, *J.*, 1949, 315; 1950, 2103; Owen and Robins, *J.*, 1949, 320). In 2-phenyl-5-toluene-*p*-sulphonyloxy-1 : 3-dioxan (I), which reacts readily, the tosyl group is in a six-membered ring with only one other substituent. In 2 : 5-ditosyl 1 : 4-3 : 6-dianhydro-D-mannitol each tosyl group is in a five-membered ring and, though adjacent to another ring, is still moderately reactive. In 1 : 3-4 : 6-dimethylene 2 : 5-ditosyl dulcitol, however, the tosyl groups are in six-membered rings and adjacent to another ring; they show little reactivity. Finally, when a six-membered ring is heavily substituted, as in the sugar pyranosides, the reaction becomes very difficult. Nevertheless, under vigorous conditions, it is possible to exchange a tosyloxy-group even in an inositol (unpublished result). When, further, the tosyl group is in a ring to which other rings are fused, as in acetals of sugar pyranosides, the reaction becomes too slow to be carried out under practical conditions.

A comparison of the three epimeric 2 : 5-ditosyl 1 : 4-3 : 6-dianhydro-hexitols shows in a particularly striking manner that steric factors prevent the exchange of certain tosyloxy-groups. As mentioned earlier, both tosyloxy-groups are readily exchanged in 2 : 5-ditosyl 1 : 4-3 : 6-dianhydro-D-mannitol (X) but only one reacts in the corresponding D-sorbitol compound (XI) (Hockett *et al.*, *loc. cit.*). 2 : 5-Ditosyl 1 : 4-3 : 6-dianhydro-L-iditol (IX) has now been tested and both tosyloxy-groups have been found to be quite unreactive. After this work was finished, a paper by Wiggins and Wood (*J.*, 1951, 1180) described a more extensive comparison of these hexitol dianhydrides. They have studied the reaction of the dianhydro-hexitols with thionyl chloride and the reaction of their dimethanesulphonates with sodium iodide and with lithium chloride. The ease of reaction in all cases shows the same gradation: two methanesulphonyl or hydroxyl groups are exchanged in the mannitol derivative, only one in the sorbitol derivative, and, under the same conditions, no reaction occurs with the compounds derived from iditol.

An explanation of these facts is suggested by a study of molecular models. The three anhydrides differ only in the configuration of $C_{(2)}$ and $C_{(5)}$. They all contain two fused five-membered rings inclined to each other, forming a V-shaped molecule. Since all the above reactions involve attack on the molecule by a negative ion and removal of a group as a negative ion, they probably occur by the S_N2 mechanism, *i.e.*, an approach of the entering atom to the face of the carbon opposite to the group to be displaced. If that face is on the inside of the V, the attack is sterically hindered.

In ditosyl dianhydroiditol both tosyl groups are on the outside of the V; an inspection

of Fischer–Hirschfelder atomic models shows that any approach to the opposite sides of the carbons, on the inside of the **V**, is obstructed. In ditosyl dianhydromannitol the two tosyl groups are attached to the inside of the **V** and attacking groups can approach without steric impediment. In dianhydrosorbitol, $C_{(2)}$ has the configuration of the iditol, and $C_{(5)}$ that of the mannitol derivative; the reaction is therefore hindered at $C_{(2)}$ but not at $C_{(5)}$.

It is clear from these results that any evidence on the position of tosyl groups, derived from the iodine exchange reaction, should be treated with suspicion unless the comparison is made between primary and secondary tosyl compounds of otherwise similar structural features.

It was not the purpose of this work to isolate the iodine compounds resulting from the exchange reaction. In a few cases, however, the mixture was worked up to give syrups which failed to crystallise and could not be distilled *in vacuo* without decomposition. They contained iodine but less than the required amount.

The reactivity of tosyloxy-groups in open-chain polyhydric alcohols suggests that secondary iodo-derivatives of reducing sugars might be prepared by this reaction if the sugars were in the open-chain form, *e.g.*, as mercaptals. Work is in progress to test this possibility.

Experimental

(M. p.s are corrected. Microanalyses by Mrs. E. Bielski, of this Department, and by Dr. W. Zimmermann, Commonwealth Scientific and Industrial Research Organisation, Melbourne.)

2-*Phenyl*-5-*toluene*-p-*sulphonyloxy*-1 : 3-*dioxan* (1 : 3-*Benezylidene* 2-*Tosyl Glycerol*) (I).—**1 : 3-**Benzylidene glycerol (6·5 g.) (Hill, Whelen, and Hibbert, *J. Amer. Chem. Soc.*, 1928, **50**, 2235) was dissolved in dry pyridine (10 ml.) and toluene-*p*-sulphonyl chloride (8 g.) was added. After 12 hours the solution was poured into water, and the precipitated solid was filtered off and recrystallised from methanol, to give the *toluene*-p-*sulphonate* (7·5 g., 62%), m. p. 125° (Found : C, 61·1; H, 5·5; S, 9·3, 9·1. $C_{17}H_{18}O_5S$ requires C, 61·1; H, 5·4; S, 9·6%).

6-*Benzoyl* 1 : 3-2 : 4-*Diethylidene* 5-*Tosyl* D-*Sorbitol* (VIII).—6-Benzoyl 1 : 3-2 : 4-diethylidene D-sorbitol (10 g.) (Sullivan, *J. Amer. Chem. Soc.*, 1945, **67**, 837) was dissolved in dry pyridine (150 ml.), toluene-*p*-sulphonyl chloride (7 g.) added, and the mixture set aside for 3 days. The solution was then poured into water (1 l.). The precipitated solid was filtered off, dried, and recrystallised from light petroleum (1500 ml.), to give *6-benzoyl* **1 : 3-2 : 4-***diethylidene* **5-***tosyl* D-*sorbitol* as fine needles (9·9 g., 68%), m. p. 121°, $[\alpha]_D^{23}$ + 5·5° (*c*, 8·1 in chloroform) (Found : C, 58·6; H, 5·9; S, 6·5. $C_{24}H_{28}O_9S$ requires C, 58·5; H, 5·7; S, 6·5%).

1 : 6-Dibenzoyl **3 : 4-***iso*propylidene **2 : 5-**ditosyl D-mannitol (VI) and **3 : 4-**diacetyl **1 : 6-**dibenzoyl **2 : 5-**ditosyl D-mannitol (IV) were prepared by Brigl and Grüner's method (*Ber.*, 1934, **67**, 1969).

1 : 2 : 3 : 4-*Tetra-acetyl* 6-*Benzoyl* 5-*Tosyl* D-*Sorbitol* (III).—**1 : 2-3 : 4-**Diethylidene **6-**benzoyl **5-**tosyl D-sorbitol (2 g.) was heated on a steam-bath with a mixture of acetic anhydride (20 ml.), acetic acid (20 ml.), and concentrated sulphuric acid (3 ml.) for 1 hour. The solution was then poured on crushed ice and set aside overnight. The precipitate was collected and recrystallised from a large volume of light petroleum, to give **1 : 2 : 3 : 4-***tetra-acetyl* **6-***benzoyl* **5-***tosyl* D-*sorbitol* (1·1 g., 45%), m. p. 98°, $[\alpha]_D^{23}$ + 21·8° (*c*, 6·85 in ethyl acetate) (Found : C, 55·4; H, 5·4; S, 5·3, 5·5. $C_{28}H_{32}O_{13}S$ requires C, 55·3; H, 5·3; S, 5·3%). The compound slowly deliquesced and gave a solution that smelt strongly of acetic acid.

1 : 2-6-*Tribenzoyl* 3 : 4-*Benzylidene* 5-*Tosyl* D-*Mannitol* (VII).—**1 : 2 : 6-**Tribenzoyl **3 : 4-**benzylidene D-mannitol (2·4 g.) (Brigl and Grüner, *Ber.*, 1933, **66**, 931) was dissolved in dry pyridine (10 ml.) and treated with toluene-*p*-sulphonyl chloride (3 g.) at room temperature. After 4 days the mixture was poured into water, and the precipitated solid was recrystallised from methanol, to give **1 : 2 : 6-***tribenzoyl* **3 : 4-***benzylidene* **5-***tosyl* D-*mannitol* (2·3 g., 76%) as long feathery needles, m. p. 117°, $[\alpha]_D^{23}$ +6·0° (*c*, 8·2 in chloroform) (Found : C, 66·8; H, 5·3; S, 4·3. $C_{41}H_{36}O_{11}S$ requires C, 66·8; H, 4·9; S, 4·4%).

1 : 3 : 4-6-*Tetra-acetyl* 2 : 5-*Ditosyl Dulcitol* (V).—**1 : 3-4 : 6-**Dibenzylidene **2 : 5-**ditosyl dulcitol (8 g.) (Hann, Haskins, and Hudson, *J. Amer. Chem. Soc.*, 1942, **64**, 132), acetic anhydride (250 ml.), acetic acid (100 ml.), and concentrated sulphuric acid (6 ml.) were heated on a steam-bath until all the solid had been dissolved (1 hour). The solution was allowed to cool and then poured on crushed ice (1500 g.), and the precipitated solid was filtered off. On recrystallisation from a large volume of ethanol, **1 : 3 : 4 : 6-***tetra-acetyl* **2 : 5-***ditosyl dulcitol* was obtained as

needles (6·2 g., 78%), m. p. 169° (Found: C, 51·1; H, 5·3; S, 10·0. $C_{28}H_{34}O_{14}S_2$ requires C, 51·1; H, 5·2; S, 9·7%).

2 : 5-*Ditosyl Dulcitol* (II).—1 : 3 : 4 : 6-Tetra-acetyl 2 : 5-ditosyl dulcitol (2 g.) was suspended in a mixture of methanol (50 ml.) and hydrochloric acid (20 ml.; 15%) and boiled under reflux for 3 hours. The solution was cooled, neutralised with silver carbonate, filtered, saturated with hydrogen sulphide, and filtered again. It was then evaporated to dryness under reduced pressure and the residue recrystallised from a small volume of ethanol, to give 2 : 5-*ditosyl dulcitol* (0·8 g., 34%), m. p. 163° (decomp.) (Found: C, 49·5; H, 4·9; S, 13·5. $C_{20}H_{26}O_{10}S_2$ requires C, 49·0; H, 5·3; S, 13·1%).

To show that the hydrolysis had not affected the tosyl groups, this compound was reacetylated. Ditosyl dulcitol (0·2 g.) and acetic anhydride (1 ml.) in dry pryidine (4 ml.), were set aside for 18 hours, the solution was then poured into water, and the product filtered off and recrystallised from ethanol, to give a substance which melted, alone and in admixture with tetra-acetyl ditosyl dulcitol, at 169°.

2 : 5-*Ditosyl* 1 : 4-3 : 6-*Dianhydro*-L-*iditol* (IX).—This was prepared from 1 : 4-3 : 6-dianhydro-L-iditol by Bashford and Wiggins's method (*J.*, 1950, 373) but was found to have different constants, namely m. p. 106°, $[\alpha]_D^{23}$ +33° (*c*, 2·0 in chloroform) (Found: C, 52·8; H, 4·8; S, 14·0, 14·2. Calc. for $C_{20}H_{22}O_8S_2$: C, 52·8; H, 4·9; S, 14·1%). Bashford and Wiggins report m. p. 90°, $[\alpha]_D$ +38·2° (*c*, 2·0 in chloroform). The dianhydro-iditol was prepared according to Wiggins's directions (*J.*, 1947, 1403), and melted at 60—62°, in agreement with Fletcher and Goepp (*J. Amer. Chem. Soc.*, 1945, **67**, 1042; 1946, **68**, 939); but the hemihydrate described by Wiggins was not obtained. To identify further the dianhydro-compound, it was converted into its dibenzoate, m. p. 109°, $[\alpha]_D^{21}$ +142°, in good agreement with both Fletcher and Goepp's and Wiggins's data.

Conditions of Replacement.—The amount of compound equivalent to 0·2 g. of sodium iodide was heated in a sealed tube with sodium iodide (0·3 g.) and dry acetone (10 ml.) for the requisite time. The tube was then opened, the contents were filtered through a sintered-glass crucible, and the precipitate was washed with acetone (2 ml.) and dried at 100° to constant weight. The crucible was then washed with water, dried, and reweighed. In only one case was there a residue and that was with 1 : 3 : 4 : 6-tetra-acetyl 2 : 5-ditosyl dulcitol (2 hours at 100°). This was the only substance insoluble in cold acetone.

Allowance was made for the solubility of sodium toluene-*p*-sulphonate in acetone (0·0012 g. per ml. at 18°, Foster *et al.*, *loc. cit.*). In those cases where the amount of sodium toluene-*p*-sulphonate is given as >100%, the value was sometimes as high as 108% which indicates the limit of accuracy obtainable with this method.

Attempted Preparation of Iodo-compounds.—Three compounds (IV, V, and VI) were treated in the following manner: The compound (1·0 g.) was heated under reflux for 1 hour with acetic anhydride (10 ml.) and sodium iodide (1·0 g.). The solution was then poured into a sodium hydrogen carbonate solution whereupon a syrup separated. The aqueous layer was decanted and the syrup washed with water until free from chloride. The syrup was then taken up in benzene, and the solution washed with sodium thiosulphate solution and then several times with water. The solvent was dried and evaporated. In each case a syrup was obtained which could not be induced to crystallise and would not distil under reduced pressure. The syrups were dried for 4 hours at 66°/0·5 mm. and analysed (Found, for 3 : 4-diacetyl 1 : 6-dibenzoyl 2 : 5-dideoxy-2 : 5-di-iodohexitol: I, 28·6. $C_{24}H_{24}O_8I_2$ requires I, 36·5%. Found, for 1 : 3 : 4 : 6-tetra-acetyl 2 : 5-dideoxy-2 : 5-di-iodohexitol: I, 32·0. $C_{14}H_{20}O_8I_2$ requires I, 44·5%. Found, for 1 : 6-dibenzoyl 3 : 4-*iso*propylidene 2 : 5-dideoxy-2 : 5-di-iodohexitol: I, 28·4. $C_{23}H_{24}O_6I_2$ requires I, 39·0%).

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200. *The Sorption of Vapours by Ferric Oxide Gel. Part III.* Aliphatic Amines.*

By Marjorie J. Brown and A. Graham Foster.

Sorption isothermals of the primary aliphatic amines, from ethyl to *n*-heptyl, and some related substances have been determined on ferric oxide gel. All show large hysteresis loops, and the general quantitative relations closely resemble those found previously with the aliphatic alcohols. The amounts (in mg./g.) of the various straight-chain amines required to form a monolayer are proportional to their molecular weights, whilst the amounts held at saturation correspond to the filling of a constant pore volume. The capillary radii, calculated by application of the Kelvin equation, are reasonably constant.

In Part I (Foster, *Proc. Roy. Soc.*, 1934, *A*, **147**, 128) sorption isothermals of the aliphatic alcohols, from methyl to *n*-butyl, on ferric oxide gel were described. It was thought that an investigation of the aliphatic amines might be of interest since these compounds are considerably more volatile than the corresponding alcohols and it should therefore be possible to examine a wider range of molecular size. In the present work, isothermals of the primary aliphatic amines, from ethyl to *n*-heptyl, and some related substances, *viz.*, ethylenediamine, *tert.*-butylamine, *cyclo*hexylamine, and pyridine, have been determined. All show large hysteresis loops, and the general quantitative relations closely resemble those found with the alcohols, *e.g.*, the amounts held at saturation correspond to the filling of a constant pore volume, the amounts required to form a complete monolayer correspond to a constant number of molecules, and the capillary radii calculated by means of the Kelvin equation are reasonably constant.

Experimental

The technique described in Part I was used except with ethylamine, for which a modification of Goldmann and Polanyi's method (*Z. physikal. Chem.*, 1928, *A*, **132**, 313) was employed. The ethylamine was distilled from sodium in a Claisen flask, through a Quickfit condenser with joints lubricated with Silicone grease, into tube *A* (Fig. 1A) containing fresh sodium. The condenser and guard tube were then sealed off at *B* whilst *A* was cooled in liquid air and the system thoroughly evacuated; *A* was then left at room temperature until effervescence due to reaction of moisture with sodium had ceased. The ethylamine was again frozen, and the gas pumped off. This treatment was repeated until no further gas was evolved and the dry amine was then distilled into another bulb *C*. After the apparatus had been sealed at *D*, a first fraction of ethylamine was condensed in *E* and removed by sealing. The middle fraction was then condensed in a series of small bulbs *F*, which were then sealed and stored in a refrigerator. One of these bulbs was then weighed and placed in the tube *G* (Fig. 1B), where it could be broken *in vacuo* by means of the iron-cored tube *H* and an external magnet ; *G* was connected *via* the mercury-actuated sintered-glass cut-offs J_1, J_2, J_3, and J_4 to a bulb *K*, mercury manometer *L*, a set of small tubes *M*, and finally to the mercury-vapour pump and McLeod gauge. Since the sintered-glass disc reduced the rate of pumping considerably, a by-pass *N* of wide bore tubing was used to evacuate the left-hand side of the system.

A known weight of previously evacuated gel was placed in the bulb *K*, which was then sealed on to the apparatus and evacuated at 150°. After prolonged evacuation and heating of the entire glass apparatus, the constrictions at *O* and *P* were sealed after all cut-offs had been raised. Bulb *F* was broken, and the ethylamine transferred completely to *K* by cooling the latter in liquid air with J_1 open. The portion *G* was then removed by sealing off at *Q* and the pieces of glass from the broken bulb *F* were collected and weighed in order to obtain the total weight of ethylamine introduced into the system. Cut-off J_2 was then lowered, and the vapour pressure of ethylamine, present in excess, read on *L* whilst *K* was immersed in melting ice. By closing J_2 and opening J_3 some ethylamine was removed and condensed in one of the bulbs *M*. This removal was continued until the pressure fell just below saturation, whereupon *M* was sealed off and broken under excess of standard hydrochloric acid. After back-titration

* Part II, *J.*, 1946, 446.

with sodium hydroxide, the weight of ethylamine thus removed, and hence the amount left in the system, could be calculated. This procedure was repeated, known weights of amine being removed in a sealed tube after each pressure reading until the pressure fell to a few mm. The bulb K was then heated to 150°, and the residual ethylamine collected and titrated.

Owing to the high vapour pressure of ethylamine and the comparatively large volume of connecting tubing between the bulb K and manometer L, it could not be assumed that all the ethylamine in the system was actually adsorbed by the gel in K. This " dead-space " correction was determined directly by performing a " blank " run in which the gel was replaced by an equal volume of mercury, and a graph was constructed showing the weight of amine in the dead space at a given pressure. The high vapour pressure of ethylamine also resulted in mercury being forced through the sintered discs in the cut-offs, and subsequently blocking the apparatus. This difficulty was largely overcome by providing sumps into which the mercury so displaced could drain and from which it could be returned, *via* a tap, to the cut-off reservoir.

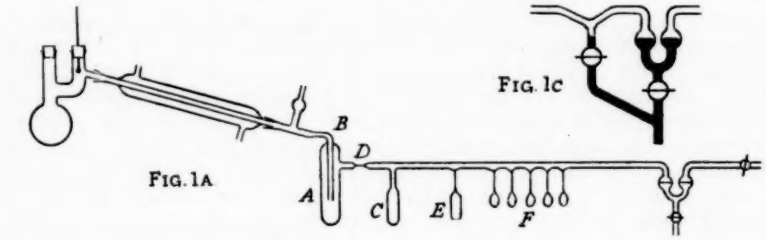


FIG. 1A

FIG. 1C

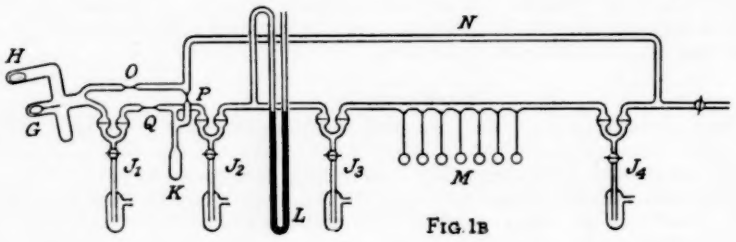


FIG. 1B

This device is illustrated in Fig. 1c. No great accuracy is claimed for the experimental method, owing to the high dead-space correction and to the cumulative effect of titration errors, and unfortunately no ascending points can be determined.

Vapour-pressure and Surface-tension Measurements.—No vapour-pressure data are recorded in the literature for the higher amines, and direct manometric measurements were therefore made on purified samples. After preliminary drying and fractionation, the amine was, as with ethylamine, distilled from sodium and finally condensed in a small bulb attached to a mercury manometer, which was sealed off and immersed in a thermostat, and the saturation pressure was read directly by means of the cathetometer.

No literature value could be found for the surface tension of *tert.*-butylamine or *n*-heptylamine. Data for these substances were obtained by the capillary-rise method, by distillation *in vacuo* into a U-tube with capillary limbs of about 0·05 and 0·2 mm. diameter, in which a differential capillary rise of 10—20 mm. could be obtained. The apparatus was calibrated with water and benzene.

The physical constants required in order to calculate the pore radius from the Kelvin equation are the density (d), surface tension (γ) and vapour pressure (v. p.). The values chosen from the literature, together with those determined in the present research, are collected in Table 1.

Surface-area Measurements.—The surface area of the gel was determined by a modification of the standard Brunauer–Emmett–Teller (B.E.T.) method, oxygen being used instead of nitrogen, in the apparatus described by Gregg and Sing (*J. Phys. Coll. Chem.*, 1951, **55**, 592). From the slope and intercept of the B.E.T. plot the monolayer capacity V_m was found to be 39·5 c.c. (N.T.P.) of oxygen per g., and the constant c of the B.E.T. equation had the value 42·2.

The calculated surface area will depend on the value taken for the cross-sectional area of the oxygen molecule. Molecular areas are usually calculated from the liquid density by means of an equation of the type $\sigma^2 = F(M/Nd)^{2/3}$. Livingston (*J. Amer. Chem. Soc.*, 1944, **66**, 571) tabulates values of F for different types of packing. The value 1·260 for square close-packing

TABLE 1.

Substance	Temp.	d_4^t	γ (dynes/cm.)	V. p. (mm. Hg)
Ethylamine	0°	0·7056 [a]	22·68 [b]	369·9 [c]
n-Propylamine	0	0·7382 [d]	25·14 [d]	94·9 *
n-Butylamine	25	0·7369 [d]	23·74 [d]	95·7 *
n-Amylamine	25	0·7498 [d]	24·66 [d]	31·8 *
n-Hexylamine	25	0·7618 [d]	25·85 [d]	9·69 *
n-Heptylamine	35	0·7635 [d]	25·96 *	6·46 *
Ethylenediamine	25	0·8938 [d]	41·42 [g]	13·42 [f]
tert.-Butylamine	0	0·7137 *	31·32 *	116·2 *
*cyclo*Hexylamine	25	0·8629 [d]	31·19 [d]	9·46 *
Pyridine	25	0·9779 [g]	36·48 [h]	20·18 [i]

* Personal measurements. (*a*) Swift, *J. Amer. Chem. Soc.*, 1942, **64**, 115. (*b*) Swift and Calkins, *ibid.*, 1943, **65**, 2145. (*c*) Pohland and Mehl, *Z. physikal. Chem.*, 1933, **164**, *A*, 45. (*d*) Vogel, *J.*, 1948, 1825. (*e*) Rudnew, *Bull. Soc. chim.*, 1880, **33**, 297. (*f*) Stull, *Ind. Eng. Chem.*, 1947, **39**, 518. (*g*) Walden, Audrieth, and Birr, *Z. physikal. Chem.*, 1932, **160**, *A*, 337. (*h*) Timmermans, "Physico-Chemical Constants of Pure Organic Compounds," Elsevier, New York, 1950. (*i*) Van der Meulen and Mann, *J. Amer. Chem. Soc.*, 1931, **53**, 451.

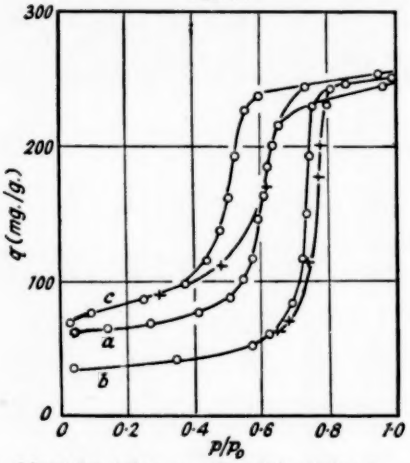
TABLE 2.

Ethylamine (0°)													
q (mg./g.)...	245	237	232	232	205	182	110	76	62	47	40	38	
p/p_0	0·95	0·85	0·77	0·70	0·68	0·66	0·63	0·52	0·42	0·26	0·16	0·03	
n-*Propylamine* (0°)													
q (mg./g.)...	238	235	226	209	152	124	87	59	51	68	96	147	224
p/p_0	0·99	0·76	0·64	0·61	0·59	0·57	0·47	0·11	0·02	0·28	0·53	0·64	0·69
q (mg./g.)...	235												
p/p_0	0·80												
n-*Butylamine* (25°)													
q (mg./g.)...	258	243	230	206	183	150	120	102	94	74	67	65	92
p/p_0	0·99	0·62	0·61	0·59	0·58	0·55	0·52	0·47	0·44	0·18	0·06	0·02	0·43
q (mg./g.)...	114	152	244										
p/p_0	0·52	0·67	0·74										
n-*Amylamine* (25°)													
q (mg./g.)...	246	236	231	190	160	140	116	104	100	87	78	71	
p/p_0	0·90	0·57	0·56	0·52	0·50	0·48	0·44	0·40	0·35	0·25	0·09	0·03	
n-*Hexylamine* (25°)													
q (mg./g.)...	254	247	241	232	210	150	110	101	88	81	99	106	129
p/p_0	0·95	0·75	0·59	0·49	0·47	0·44	0·37	0·30	0·16	0·06	0·31	0·39	0·47
q (mg./g.)...	209	239	256										
p/p_0	0·59	0·69	0·98										
n-*Heptylamine* (35°)													
q (mg./g.)...	256	248	246	238	225	193	186	135	116	103	94		
p/p_0	0·96	0·58	0·47	0·43	0·40	0·38	0·38	0·33	0·27	0·15	0·03		
Ethylenediamine (25°)													
q (mg./g.)...	307	300	296	287	283	253	256	185	130	109	102	82	66
p/p_0	0·97	0·88	0·76	0·61	0·56	0·53	0·52	0·49	0·43	0·40	0·39	0·32	0·19
q (mg./g.)...	59	54	67	77	104								
p/p_0	0·12	0·05	0·23	0·32	0·44								
tert.-*Butylamine* (0°)													
q (mg./g.)...	236	231	221	201	159	121	97	73	53	58	43	78	119
p/p_0	1·0	0·80	0·59	0·57	0·55	0·52	0·48	0·40	0·17	0·09	0·01	0·43	0·55
cyclo*Hexylamine* (25°)													
q (mg./g.)...	286	284	275	266	244	190	145	120	98	92	82	73	70
p/p_0	0·99	0·77	0·51	0·46	0·44	0·42	0·46	0·36	0·30	0·27	0·18	0·04	0·03
Pyridine (25°)													
q (mg./g.)...	325	319	309	314	305	280	225	155	113	81	63		
p/p_0	1·0	0·89	0·74	0·82	0·66	0·54	0·49	0·44	0·36	0·18	0·03		
Oxygen (90·3° K)													
Vol. (c.c. N.T.P./g.) ...	27·9		34·1		38·5		41·0		47·0		51·3	58·7	68·7
p/p_0	0·038		0·081		0·126		0·155		0·226		0·278	0·356	0·445

makes the above equation correspond to the relation $\sigma = 1{\cdot}33 \times 10^{-8}\ (M/d)^{1/3}$, which was used previously in this work and is retained throughout the present paper. The value 1·091 for hexagonal close-packing gives the relation used by Emmett and Brunauer (*ibid.*, 1937, **59**, 1553) upon which most of the surface-area values determined by the B.E.T. method are based. These two relations give 16·3 and 14·1 Å², respectively, for oxygen, whence the surface area of the gel is either 175 or 151 sq. m. per g.

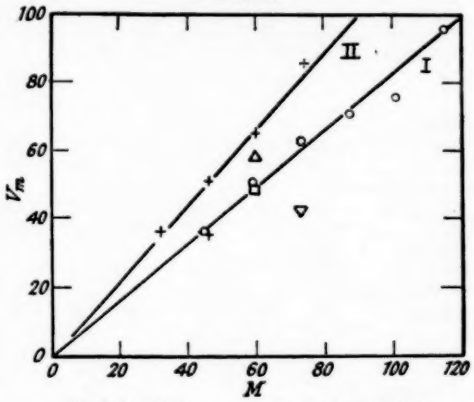
Results.—The experimental data are recorded in Table 2, which gives the amount adsorbed (q) in mg./g. of gel at various relative pressures (p/p_0). The gel used here was the remainder of the batch prepared by Broad and Foster in 1938 and used by them in Part II (*loc. cit.*). In Fig. 2 isothermals of ethyl alcohol determined in 1938 and in 1949 (present work) are compared. The marked shift due to ageing of the gel indicates an increase in pore radius and a decrease in surface area, the saturation volume remaining unchanged. A typical isothermal for the amines is also shown in Fig. 2. The isothermals have the same features as those of the alcohols and all show large reproducible hysteresis loops. Comparative data are summarised in Table 3.

FIG. 2.



Adsorption points +; *Desorption points* ○.
(*a*) EtOH, 1939; (*b*) EtOH, 1949;
(*c*) n-*Amylamine.*

FIG. 3.



+ *Alcohols*, 1936. ○ *Amines*, 1949.
△ iso*Propyl alcohol.* ▽ tert.-*Butylamine.*
□ *Ethylenediamine.*

TABLE 3.

1	2	3	4	5	6	7	8	9	10	11	12
	t	q_s (mg./g.)	V_s (mm.³/g.)	V_m (mg./g.)	V_m/q_s (%)	V_m/M (m.-moles/g.)	$10^{19}V_m\sigma^2/M$	p_i/p_0	r (Å)	$r+2\sigma$ (Å)	V_h/V_m
Et·NH_2	0°	246	314	36	15	0·80	22·65	0·66	31	42	—
Pr^n·NH_2	0	238	322	50	21	0·85	27·95	0·58	32	44	1·7
Bu^n·NH_2	25	252	342	64	25	0·87	32·98	0·58	34	46	1·5
n-C_5H_{11}·NH_2	25	248	331	70	28	0·80	33·82	0·51	35	48	1·5
n-C_6H_{13}·NH_2	25	256	336	76	30	0·75	34·52	0·46	35	49	1·4
n-C_7H_{15}·NH_2	35	256	335	96	37	0·83	41·65	0·39	32	46	—
$(CH_2$·$NH_2)_2$ ...	25	310	347	49	16	0·82	24·02	0·51	33·5	45	1·5
Bu^t·NH_2	0	237	332	42	18	0·57	22·08	0·55	32	46	1·9
C_6H_{11}·NH_2 ...	25	284	329	68	24	0·69	28·05	0·43	34	47	1·4
C_5H_5N	25	328	330	58	18	0·73	24·15	0·48	34	45	—
H_2O	25	328	329	36	11	2·0	24·38	0·73	34	41	2·5
EtOH	25	252	321	35	14	0·76	20·31	0·74	34	44	1·6

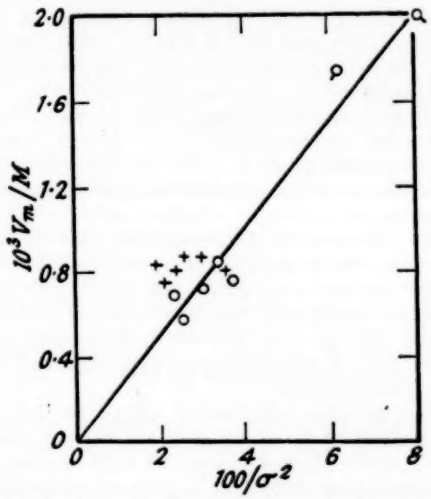
DISCUSSION

Saturation Volumes.—The amounts (q_s) held at saturation are recorded in col. 3 of Table 3. The corresponding volumes (V_s), calculated from the normal liquid density, are approximately constant and show maximum deviations of ±5% from the mean value 330 mm.³/g.

Monolayer Capacity.—Col. 5 gives the amounts (V_m) required to form a complete monolayer, estimated, as in Part II, by the " point A " method. For the straight-chain amines, V_m is clearly proportional to the molecular weight as shown by the approximate constancy of the values of V_m/M in col 7. In Fig. 3, curve I, V_m for these amines is plotted against M, and curve II shows the corresponding relation for the alcohols investigated in Part I. The difference in slope is due to the ageing of the gel, and since the 1949 point for ethyl alcohol falls exactly on curve I it is reasonable to suppose that if both the alcohols and the amines had been examined on the same sample of gel, the two curves would coincide. It is noteworthy that, just as the point for *iso*propyl alcohol falls below curve II, so also does that for *tert.*-butylamine fall below curve I. Further, the point for ethylenediamine falls exactly on the latter curve. The low V_m/M values for all the other substances except water indicate that these points, which have been omitted from Fig. 3, would fall well below curve I.

In Part I it was assumed that the constancy of V_m/M indicated a definite orientation, similar to that of the long-chain fatty acids on water, with a cross-sectional area of the

FIG. 4.



+ *Normal amines*; ○ O_2; ○ H_2O; ○ *Other compounds.*

FIG. 5.

order 20 Å^2 per molecule, independent of the length. On this basis, the slope (0·82) of curve I corresponds to a surface area of 99 sq. m. per g., which is considerably lower than either of the values derived by the B.E.T. method from the oxygen isothermal. In order to obtain agreement with the lower of the last two values it would be necessary to assume a sectional area of at least 30 Å^2 per molecule.

It was shown by Broad and Foster (*J.*, 1945, 369) that on silica gel the values of V_m/M for the alcohols are not constant but proportional to $1/\sigma^2$, *i.e.*, the quantity $V_m\sigma^2/M$ is constant. This corresponds to the expression $(V_m/M)(M/d)^{2/3}$ suggested by Goldmann and Polanyi (*loc. cit.*) for the covering of a constant surface area. A similar behaviour is shown by the amines on silica gel (Brown and Foster, *J. Phys. Coll. Chem.*, in the press), where it is found that the best curve through the plot of V_m/M against $1/\sigma^2$ is a straight line which also passes through the points for water and oxygen. Fig. 4 shows a similar graph for the substances investigated in the present work on ferric oxide gel. The points for the normal amines naturally lie round a constant value of V_m/M, but the best curve through the other points, including those for oxygen and water, is a straight line of slope $2{\cdot}56 \times 10^{-18}$ mole cm.$^{-2}$, which multiplied by N gives a specific surface area of 155 sq. m. The value of σ^2 corresponding to the constant number of moles of the straight-chain amines adsorbed is

31 Å², which is therefore the apparent cross-sectional area of these substances when adsorbed on ferric oxide.

The discrepancy between this and the value 20 Å² usually found for surface films may be due to the curvature of the surface on which adsorption takes place. Then, considering the rather crude model represented by Fig. 5, in which cylindrical molecules of cross-sectional area A_1 are adsorbed with their *heads* forming a close-packed assembly, it is clear that the *tails* are no longer in contact with one another and, so far as the covering of the adsorbent surface is concerned, the molecules have an effective cross-section A_2 given by $A_2/A_1 = (r_2/r_1)^2$. If r_1 is taken as 35 Å, then, for a molecule 10 Å long, r_2 will be 45 Å and $A_2 = 20(9/7)^2 = 33$ Å². Similarly, a molecule 5 Å long would have an effective area of 25 Å², so that the observed effective area of 31 Å² is quite consistent with this explanation, although the predicted variation with chain length is not observed.

Capillary Radii.—The relative pressures at the point of inflexion of the desorption branch of the hysteresis loop are recorded in col. 9 of Table 3, and the corresponding pore radii, calculated by means of the Kelvin equation, are given in col. 10. Unfortunately, these points of inflexion are much less clearly defined than in the earlier parts of this work, an effect presumably due to ageing of the gel. The radii lie within ±3 Å of the mean value 34 Å and show no significant variation with the size of the adsorbed molecule. A similar conclusion was drawn from the data for the alcohols in Part I, where it was tentatively suggested that there was a tendency for the adsorbed layer to build up to a constant thickness before the advent of capillary condensation. On the other hand, the data of Part II, in which mainly non-polar liquids were examined, supported the view that two adsorbed layers were present before condensation, and the values of $r + 2\sigma$ were reasonably constant, showing variations of ±2 around a mean of 32 Å. The corresponding figures for the amines, recorded in col. 11, show variations of ±4 around a mean of 45 Å, which is slightly less satisfactory but still reasonable.

In the systems investigated in Part II, the amount (V_h) adsorbed when hysteresis begins is usually rather more than twice the monolayer capacity (V_m), and the ratio V_h/V_m varies from 2·1 to 2·7. The values for the alcohols are significantly lower, *e.g.*, 1·3 for *n*-butyl alcohol, and the figures of col. 12 show clearly that this is true also of the amines. This is most likely a consequence of the very close packing involved in the formation of an oriented monolayer which is not possible with the less polar liquids, and suggests that the second layer of amine or alcohol molecules is not oriented.

In a parallel investigation of these amines on silica gels (Brown and Foster, *loc. cit.*) it has been found that the size of the hysteresis loop decreases as the molecular diameter increases, and on one sample of gel with a Kelvin radius of approx. 15 Å, hysteresis occurs only with the lower amines and is not observed with molecules larger than *n*-butylamine. On the coarser ferric oxide gel used here, little variation is observed in the size of the loop.

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201. *Some Measurements of the Self-diffusion Coefficients of Liquids.*

By K. Graupner and E. R. S. Winter.

By use of deuterium as tracer element, the self-diffusion coefficients of water, benzene, bromoethane, and ethanol have been measured over the temperature range 15—45°. For water, some measurements have also been made by using ^{18}O.

Self-diffusion measurements have been reported upon only two liquids, namely, lead (Groh and Hevesy, *Ann. Physik*, 1920, **63**, 85) and water (Temkin, *Nature*, 1935, **136**, 552; Orr and Butler, *J.*, 1935, 1273; Lamm, *Nova Acta Regiae Soc., Upsala*, 1937, **10**, No. 6; Rögener, *Z. Electrochem.*, 1941, **47**, 164; Wang, *J. Amer. Chem. Soc.*, 1951, **73**, 510, 4181). This lack of experimental work is somewhat surprising since there is a large and growing body of work upon self-diffusion coefficients in solids, and recently those of a number of gases have been measured (Hutchinson, *Phys. Rev.*, 1947, **72**, 1256; Winn, *ibid.*, 1948, **73**, 698; 1950, **80**, 1024; Winter, *Trans. Faraday Soc.*, 1951, **47**, 342). With the present ready availability of tracer isotopes, both stable and radioactive, many more experimental measurements upon self-diffusion may be expected: this paper presents data for the self-diffusion coefficients of water, benzene, bromoethane, and ethanol, over the temperature range 15—45°. Deuterium has been used as the tracer element, and in the case of water some observations have also been made by using the oxygen isotope ^{18}O.

Experimental

Materials.—Monodeuterobenzene: Deuterium oxide (29% D_2O; 0·48 g.-mol.) was slowly added to a stirred ethereal solution of phenylmagnesium bromide (0·48 g.-mol.) cooled in ice-water. The ether and deuterobenzene were distilled off, finally *in vacuo*, and carefully fractionated; the yield was 24 g. (57%) of benzene containing 1·7% of ether. The ether was removed by treatment with 60% perchloric acid (Best and Wilson, *J.*, 1946, 239). Final purification was effected by successive distillations *in vacuo* from phosphoric oxide; the benzene obtained contained 25% of C_6H_5D. The normal benzene used was Baker's C.P. thiophen-free, distilled *in vacuo* from phosphoric oxide.

2-Deuterobromoethane, $CH_2D{\cdot}CH_2Br$, was prepared by addition of deuterium bromide to ethylene on a bismuth bromide–asbestos catalyst (Wibaut, Dickmann, and Rutgers, *Rec. Trav. chim.*, 1928, **47**, 477). Yields of about 24% were found, in contrast to the 80—90% reported by Wibaut *et al.* The resulting ethyl bromide and the normal material (May and Baker) were purified by distillation from phosphoric oxide, the fraction, b. p. 38—40°, being collected.

Ethyl deuteroxide was prepared by adding 1·6 ml. of 3% D_2O to 29 ml. of dry " AnalaR " ethyl alcohol, followed by drying with barium oxide and twice with anhydrous copper sulphate. The barium oxide treatment reduces the water content to 0·6% (Smith, *Ind. Eng. Chem. Anal.*, 1929, **1**, 72): the first batch of copper sulphate became slightly blue, but the second did not, so the alcohol contained certainly less than 0·6% water. The light alcohol used (Burnett's) had been kept for some months over anhydrous copper sulphate; it boiled at 78°: the ethyl deuteroxide was distilled *in vacuo* from the copper sulphate immediately before use.

Combustions.—Samples of benzene were burnt by vapourising the liquid slowly in a stream of dry oxygen which was passed over copper oxide at 800° with a contact time of about 20 seconds. The combusion water was collected in traps cooled in solid carbon dioxide and further purified by distillation *in vacuo* over granular copper oxide at 700°. Bromoethane and ethanol were similarly burnt in a rapid stream of oxygen over asbestos at 800°. In spite of the known exchange reaction of hydrogen from asbestos (Wilson and Wylie, *loc. cit.*), we found no trouble from this cause under our experimental conditions: our asbestos was outgassed at 800° before use, and this treatment may remove the reactive hydrogen. Excess of bromine was removed from the combusion water from ethyl bromide by treatment with carefully dried silver oxide: similar treatment was found necessary for the combusion water from ethanol before consistent density measurements could be obtained.

Deuterium Analyses.—The deuterium contents of the relatively highly enriched compounds obtained by the synthetic methods outlined above, and that of the water used, were determined by pycnometer: both the Parker and Parker pycnometer (*J. Physical Chem.*, 1925, **29**, 130)

and the Fontana and Calvin semi-micropycnometer (*Ind. Eng. Chem. Anal.*, 1942, **14**, 185) were used. The results so obtained were confirmed by accurately diluting a small quantity of the heavy material with sufficient of the normal compound to give <1 atom % of D, and then determining the deuterium content of the water obtained from the diluted material by combustion. The deuterium content of the original heavy compound was calculated by use of Weldon and Wilson's equation (*J.*, 1946, 235). Proper corrections were made throughout to allow for variations in ^{18}O and D content of the reference compounds and reagents (for a detailed account see Graupner, Thesis, London, 1950). The deuterium contents of samples of water containing <1% of D_2O were measured by the semi-micro-silica float method of Briscoe *et al.* (*J.*, 1934, 1207; 1937, 1492; Spoor, Thesis, London, 1938). All water samples were first purified by distillation *in vacuo* from a trace of potassium permanganate and sodium peroxide and then from a trace of phosphoric oxide as described by Spoor. $H_2{}^{18}O$ contents were determined in the same manner.

Diffusion Measurements.—Two Northrop–McBain cells (McBain and Dawson, *Proc. Roy. Soc.*, 1935, **148**, 32; cell type I), made from Pyrex glass, were used: they had capacities of approx. 4 and 11 ml. and porosities G3 and G4, respectively. All diffusion runs lasted some 18 hours: for each compound one run at each temperature was carried out in both cells, and the mean of the two results recorded (except for water at 25° and the two experiments with $H_2{}^{18}O$, all of which were performed in cell I only). The duplicate measurements were in reasonable agreement, except in the case of bromoethane where the differences were much larger, owing we believe, to the difficulty of handling and of burning this relatively volatile liquid: the results are summarised in Table 1. The diffusion runs were followed by determining the density

TABLE 1. *Self-diffusion measurements.*

Temp.	Liquid	$D \times 10^5$; cm.^{2} sec.$^{-1}$ Cell I	Cell II	Mean
15°	D_2O–H_2O	1·60	1·65	1·62 ± 0·03
25	D_2O–H_2O	2·04	—	2·04
35	D_2O–H_2O	2·69	2·77	2·73 ± 0·04
45	D_2O–H_2O	3·42	3·25	3·34 ± 0·08
25	$H_2{}^{18}O$–H_2O	2·09	—	2·09
45	$H_2{}^{18}O$–H_2O	3·20	—	3·20
15	C_6H_5D–C_6H_6	1·88	1·89	1·88 ± 0·01
25	C_6H_5D–C_6H_6	2·21	2·10	2·15 ± 0·05
35	C_6H_5D–C_6H_6	2·43	2·37	2·40 ± 0·03
45	C_6H_5D–C_6H_6	2·61	2·74	2·67 ± 0·06
15	C_2H_4DBr–C_2H_5Br	3·23	3·97	3·60 ± 0·37
22·5	C_2H_4DBr–C_2H_5Br	4·06	3·55	3·80 ± 0·76
30	C_2H_4DBr–C_2H_5Br	4·15	3·77	3·96 ± 0·19
15	$C_2H_5{\cdot}OD$–$C_2H_5{\cdot}OH$	0·79	0·81	0·80 ± 0·01
25	$C_2H_5{\cdot}OD$–$C_2H_5{\cdot}OH$	1·03	1·08	1·05 ± 0·03
35	$C_2H_5{\cdot}OD$–$C_2H_5{\cdot}OH$	1·25	1·38	1·31 ± 0·07
45	$C_2H_5{\cdot}OD$–$C_2H_5{\cdot}OH$	1·73	1·67	1·70 ± 0·03

TABLE 2. *Diffusion cell data.*

	Cell I	Cell II		Cell I	Cell II
Porosity	G3	G4	Vol. of sintered diaphragm at 20°, ml.	0·075	0·203
A/L, cm.	0·59	2·31	Cell constant, K, cm.†	0·131	0·192
Vol. of cell at 20°, ml.*	3·91	10·94			

* Excluding volume of sintered disc. † Obtained from Table 3, and equation (2).

of the combustion water, obtained as outlined above by burning samples of liquid, from the two cell compartments at the end of the diffusion. The deuterium concentrations were so chosen that the maximum deuterium content encountered was <1 atom %.

The diffusion cells were suspended from rubber tubing attached to a rigid external support inside air-thermostats surrounded by a water-thermostat. The temperature of the water-thermostat was held constant within ±0·04° over long periods, and Beckmann-thermometer readings in the air-thermostats were constant to better than ±0·001°. Information relating to the two cells is given in Table 2: the volumes of each cell and of the sintered discs of each cell were determined by filling with water and weighing. In order to perform a diffusion run, the contents of cell I were allowed to diffuse into a volume of 3·91 ml. (delivered into the bottom part of the cell by a specially made pipette), and those of cell II were allowed to diffuse into a volume of 10 ml. The cells were frequently cleaned by immersion in a beaker of chromic–sulphuric acid and heating this solution until fuming occurred: after cooling, the cells were

washed through with water and dried. This procedure led to no change in the cell constant. Silicone vacuum stop-cock grease was used on the taps of the cells.

The diffusion cells were calibrated at 25° by allowing 0·1N-potassium chloride to diffuse into water, and employing Gordon's value for $D_i^{25} = 1{\cdot}838 \times 10^{-5}$ cm.^{2} sec.$^{-1}$ (*Ann. N.Y. Acad. Sci.*, 1945, **46**, 285). The sintered discs were outgassed in the manner described by McBain and Lui (*J. Amer. Chem. Soc.*, 1931, **53**, 59), and freshly outgassed potassium chloride solution was employed in the calibration: the time allowed for the preliminary diffusion was 30 minutes. Details of the calibration results are given in Table 3, together with some figures obtained at

TABLE 3. *Diffusion with potassium chloride.*

Cell	Temp.	Time (hr.)	$KD_i \times 10^6$, sec.$^{-1}$	Cell	Temp.	Time (hr.)	$KD_i \times 10^6$, sec.$^{-1}$
I	20°	22	2·14	II	20°	17	3·13
	,,	19	2·11 mean 2·14		,,	18	3·17 mean 3·15
	,,	17	2·17				
				II	25	22	3·54
I	25	18	2·39		,,	20	3·54
	,,	23	2·42		,,	17	3·57
	,,	17	2·38		,,	18	3·50 mean 3·53
	,,	16	2·46 mean 2·41		,,	20	3·51
	,,	17	2·40		,,	16	3·53
	,,	15	2·42		,,	15	3·58

20°. The cell constants, K, were calculated from the relations:

$$\left.\begin{array}{ll} \text{for cell I,} & KD_i = (1/t) \ln (c'_f + c''_f)/(c'_f - c''_f) \\ \text{for cell II,} & KD_i = (1/t) \ln (c'_f + 10c''_f/10{\cdot}94)/(c'_f - c''_f) \end{array}\right\} \quad . \quad . \quad . \quad . \quad (1)$$

with the time, t, in seconds, c'_f, c''_f being the normalities of potassium chloride at the end of the diffusion in the upper and in the lower portion respectively of the cell.

Values of A/L in Table 2 were obtained by using:

$$K = A(V' + V'')/2{\cdot}303LV'V'' \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad (2)$$

where V', V'', are the volumes of the upper and the lower portion of the cells.

It is by no means certain that the cell constant, obtained by calibration with aqueous potassium chloride solution as above, is the correct value when the cell is used for studies upon non-polar non-conducting liquids such as benzene, ethyl bromide, etc. Such a profound change in the nature of the fluid in the sintered-glass disc could greatly alter the electrokinetic potential between the pore walls and the liquid phase, which change in potential could produce significant alterations in the electro-viscous effect (cf. Elton, *Proc. Roy. Soc.*, 1948, *A*, **194**, 259, 275; 1949, *A*, **197**, 568; Hirschler, *ibid.*, 1949, *A*, **198**, 581), in the thickness of stagnant layers, and in the speed of diffusion (see, *e.g.*, Tolliday, Woods, and Hartung, *Trans. Faraday Soc.*, 1949, **45**, 148, for the effect of adsorbed ions in cupric ferrocyanide membranes upon the activation energy for diffusion of potassium chloride through the membrane). To test this possibility, two diffusions were performed at 20° with each cell, the upper portion being filled with redistilled and outgassed carbon tetrachloride, and diffusion was allowed to take place into pure benzene. The extent of diffusion was determined by measuring refractive indices on an Abbé refractometer, and reading off concentrations (correct to $\pm 0{\cdot}2\%$) from a calibration curve constructed from the refractive indices of known mixtures of the two liquids. The values of Münter (*Ann. Physik*, 1931, **10**, 437) and of Gerlach (*ibid.*, 1931, **11**, 558) for the free diffusion of these liquids were used to calculate (by Gordon's method, *loc. cit.*, Section F), a value for D_i corresponding to our concentration ranges.

TABLE 4. *Diffusion coefficients for carbon tetrachloride–benzene at* 20°.

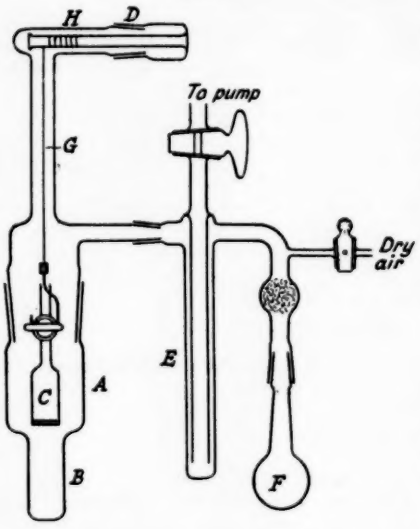
	$D^{20} \times 10^5$, cm.^{2} sec.$^{-1}$		$D^{20} \times 10^5$, cm.^{2} sec.$^{-1}$
Cell I	11·4	Cell II	1·77
,, ...	11·2	,, ...	1·74
		Calc. (Münter & Gerlach)...	1·63

Our experimental figures and the value so calculated are given in Table 4. It is evident that, owing to the relatively great density difference (carbon tetrachloride is nearly twice as dense as benzene), extensive streaming has taken place through the coarser sinter of cell I, but the value for the second cell is in reasonable agreement with the figure obtained from the measurements by Gerlach and Münter upon diffusion in the absence of a sintered diaphragm.

Time did not permit a more extensive study of this interesting and important matter, but we may perhaps conclude from these few observations that in the absence of large density differences the cell constants as determined by potassium chloride calibration are satisfactory for use with organic liquids.

In order to outgas the sintered diaphragms and to fill the cells with the deuterated liquids, which were available in only small amount and required care and economy in handling, the whole operation was carried out *in vacuo*, the evacuated cells being lowered diaphragm downwards on to the outgassed liquid with which they were to be filled. The tap of the cell was in the off position, so that when dry air was later admitted to the apparatus the liquid was slowly driven into the cell through the sintered disc. The apparatus used is shown in Fig. 1: the cell *C* was suspended from the glass rod *H* by means of the fine tungsten wire *G*, and was raised or lowered by rotation of the ground-glass socket *D*. *A* was a B55 socket, constricted to an appendix B into which was vacuum-distilled the liquid from *F*. The material in *F* was outgassed by alternately melting and freezing it with intermittent pumping, loss of material being prevented by the trap *E*.

FIG. 1.



DISCUSSION

It is interesting first to note that from our results on the diffusion of 0·1N-potassium chloride into water we may calculate D_i^{20}/D_i^{25}: taking the mean values given in Table 3, we obtain for this ratio 0·888 for cell I and 0·892 for cell II. These figures are in good agreement with that of McBain and Dawson (*loc. cit.*), *viz.*, 0·888.

Turning now to the results for water, we have plotted all the available experimental figures and our own in Fig. 2. The values reported by Orr and Butler (*loc. cit.*) were based on D_i^{20} for 0·1N-potassium chloride into water equal to $1{\cdot}68 \times 10^{-5}$ cm.^{2} sec.$^{-1}$ (Cohen and Bruins, *Z. physikal. Chem.*, 1923, **103**, 349, 404), a value which is now known to be incorrect. Taking $D_i^{25} = 1{\cdot}838 \times 10^{-5}$ cm.^{2} sec.$^{-1}$ and $D_i^{20}/D_i^{25} = 0{\cdot}888$, we find that Orr and Butler's results should be multiplied by 0·974 throughout: this has been done before plotting Fig. 2.

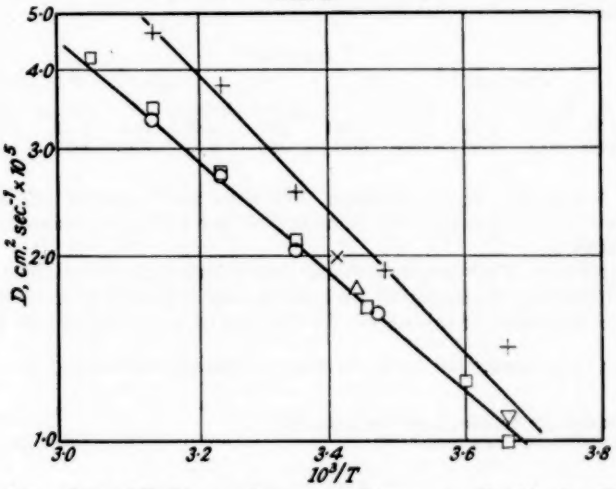
It is seen that Orr and Butler's corrected figures are still consistently greater than ours, although the experimental methods were essentially the same. Wang's results for D_2O agree quite well with ours; it should, however, be noted that the absolute values of his figures depend upon the accuracy of the method adopted to calibrate his cell. In fact, Wang assumed that Rögener's result for D_2O at 14·7° to be correct; this is a rather doubtful procedure since Rögener's diffusion technique leaves much to be desired.* However, as can be seen from the figure, Rögener's result agrees closely with our own. Lamm and Temkin's results, obtained by different experimental techniques, are also in reasonable agreement with ours. Our observation that the self-diffusion coefficient, and its activation energy, are the same whether deuterium or ^{18}O is used as the tracer element is of interest in demonstrating that the diffusion process in liquid water involves the water molecule as an entity. Wang's figures for diffusion of ^{18}O in water also show that the activation energy is the same as for the diffusion of deuterium, but differ from ours in that substantially higher rates of diffusion (some 40% faster) were found for ^{18}O. This discrepancy is difficult to account for and can only be resolved by further work. Orr and Butler have already shown that the rate of diffusion of deuterium in D_2O–H_2O mixtures

* This criticism does not apply to Wang's diffusions from capillary tubes, which yielded results in good agreement with the results obtained with the McBain cell.

is only slightly reduced in the presence of N-sulphuric acid or N-sodium sulphate, owing probably to the electrostrictive effect of the ions.

The diffusion figures for the four liquids we have studied can best be considered by using Eyring's approach to the theory of diffusion processes in liquids (Glasstone, Laidler, and Eyring, "Theory of Rate Processes," McGraw Hill, 1941), since Frenkel's equations ("Kinetic Theory of Liquids," Oxford Univ. Press, 1946) are too qualitative for our present needs, and the theories of Born and Green *et al.* (*Proc. Roy. Soc.*, 1946, **188**, *A*, 16; 1947, **190**, *A*, 455; **191**, *A*, 168; and later papers) and of Kirkwood (*J. Chem. Physics*, 1946, **14**, 180), although much more exact and detailed mathematically, are as yet

FIG. 2.



This work, ○; *Orr and Butler*, +; *Lamm*, ×; *Rögener*, △; *Temkin*, ▽; *Wang*, □.

applicable only to liquids composed of spherical monatomic molecules, and in any case lead to exceedingly complex expressions. All these theories lead to the general equation

$$D = A \exp - [E_D/\boldsymbol{R}T] \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad (3)$$

where E_D is the activation energy for diffusion. We discuss our observations by reference to Eyring's calculation of the frequency term A and of E_D. Eyring (*op. cit.*, p. 525) has developed the equation

$$D = \left(\frac{\boldsymbol{k}T}{2\pi m}\right)^{\frac{1}{2}} \frac{\lambda^2}{v_f^{\frac{1}{3}}} \exp - \left[\frac{E_V}{n\boldsymbol{R}T}\right] . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad (4)$$

where v_f is the mean free volume per molecule, given (Eyring and Hirschfelder, *J. Phys. Chem.*, 1937, **41**, 249) by

$$v_f = (\boldsymbol{R}T/\boldsymbol{N}P_V) \exp - \left[\frac{E_V + \boldsymbol{R}T}{\boldsymbol{R}T}\right] \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad (5)$$

In the above equations $\boldsymbol{k}$ is the Boltzmann constant, $\lambda^3 \approx V/N$, m the mass of one molecule, E_V the activation energy for vaporisation, P_V the vapour pressure, V the molar volume, $\boldsymbol{N}$ Avogadro's number, and n a small number, usually 3·0—3·5.

In his treatment, Eyring assumes that $n = E_V/E_\eta$, *i.e.*, that $E_D = E_\eta$; this, however, is not the case for any of the four liquids we have examined, as is shown in Table 5. We have therefore preferred in our calculations to use equation (4), but to use our experimental values of E_D instead of E_V/n. In this way, using equation (5) and values of P_V obtained from the International Critical Tables, we find the values of $A_{calc.}$ and $R = D_{obs.}/D_{calc.}$ shown in Table 6. From the values of the ratio R and from comparison of $A_{calc.}$ with $A_{obs.}$

given in Table 5, it is clear that Eyring's equations give only the order of magnitude of the diffusion coefficients; not enough liquids have been examined to decide whether there is any particular significance in the fact that for hydrogen-bonded liquids $R > 1$, whereas

TABLE 5.

	$A_{obs.}$, cm.^{2} sec.$^{-1}$	E_D	E_η kcal./g.-mol.	E_V	E_V/E_D	E_V/E_η
Benzene	$7{\cdot}75 \times 10^{-4}$	2·1	2·4	7·7	3·5	3·0
Bromoethane	$2{\cdot}86 \times 10^{-4}$	1·2	1·75	6·0	5·0	3·5
Water	$3{\cdot}78 \times 10^{-2}$	4·6	3·28	9·4	2·0	2·9
Ethanol	$2{\cdot}37 \times 10^{-2}$	4·5	3·85	9·8	2·2	2·5

[The energies of activation of vaporisation and viscous flow (E_V and E_η) were taken from Grunberg and Nissan (*Trans. Faraday Soc.*, 1949, **45**, 125).

TABLE 6.

	H_2O		$C_2H_5{\cdot}OH$		C_6H_6			H_2O		$C_2H_5{\cdot}OH$		C_6H_6	
Temp.	$10^3A_{calc.}$	R	$10^3A_{calc.}$	R	$10^3A_{calc.}$	R	Temp.	$10^3A_{calc.}$	R	$10^3A_{calc.}$	R	$10^3A_{calc.}$	R
15°	4·87	9·76	6·10	3·24	2·75	0·261	35°	4·42	10·8	6·59	2·95	2·49	0·291
25	4·63	9·90	6·52	3·06	2·62	0·278	45	4·24	10·9	6·35	3·16	2·38	0·305

$R < 1$ for the "normal" liquid benzene. We have not included bromoethane in this discussion as we do not consider the accuracy of our diffusion measurements warrants detailed calculations.

In view of this lack of agreement between theory and experiment, there is no object in pushing any further the discussion of the rate-process approach to the theory of liquids. Further detailed discussion of this nature for the case of water is given by Wang (*loc. cit.*).

One of us (K. G.) thanks the Surrey County Council for the award of a County Major Scholarship.

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202. *Studies in the Polyene Series. Part XL.* Preparation and Properties of 2-Acetyl-1 : 3 : 3-trimethylcyclohexene.*

By H. B. HENBEST and GEORGE WOODS.

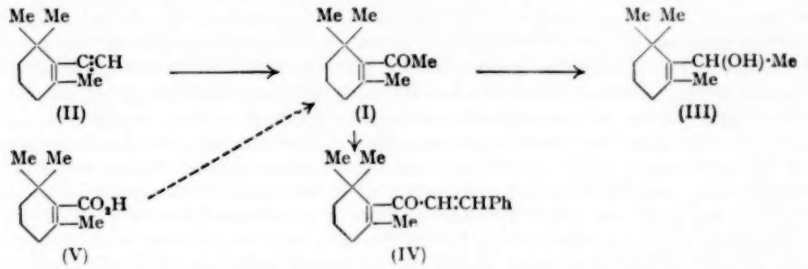
2-Acetyl-1 : 3 : 3-trimethyl*cyclo*hexene (I) has been prepared by hydration of 2-ethynyl-1 : 3 : 3-trimethyl*cyclo*hexene. This αβ-unsaturated ketone exhibits unprecedently low-intensity light absorption in the 2400 Å region, and does not yield derivatives with the usual carbonyl reagents.

IN the course of an investigation concerned with the somewhat unusual light-absorption properties of β-ionone and its derivatives, Braude, Jones, Koch, Richardson, Sondheimer, and Toogood (*J.*, 1949, 1890) noted that the introduction of a methyl group into the 2-position in 1-acetyl*cyclo*hexene markedly decreases the intensity of light absorption in the 2400 Å. region (see Table), a finding that has been confirmed by Turner and Voitle (*J. Amer. Chem. Soc.*, 1951, **73**, 1403). Chanley (*ibid.*, 1948, **70**, 244) had earlier shown that replacement of the hydrogen atoms in the 6-position of 1-acetyl*cyclo*hexene by a *gem*-dimethyl grouping only very slightly lowered the absorption intensity relatively to that of the parent compound. It therefore seemed of interest to prepare and examine the properties of 2-acetyl-1 : 3 : 3-trimethyl*cyclo*hexene (I), a compound containing both of the above-mentioned structural features, as well as being the lower vinylogue of β-ionone.

A likely method for preparing this ketone seemed to be the hydration of 2-ethynyl-1 : 3 : 3-trimethyl*cyclo*hexene (II) (Sobotka and Chanley, *ibid.*, 1949, **71**, 4136). Treatment

* Part XXXIX, *J.*, 1951, 3099.

of the freshly purified hydrocarbon either with the methanol–boron trifluoride–mercuric oxide hydration catalyst described by Hennion and Zoss (*ibid.*, 1941, **63**, 1151) or with hot formic acid gave the desired ketone (I), although the yield and quality were somewhat better in the former method. Careful fractional distillation of the product obtained by either method revealed that the main bulk was homogeneous—the product thus obtained giving correct analyses for a compound of structure (I).



The usual procedure for further purifying a carbonyl compound *via* a crystalline derivative could not be employed since the ketone did not react with semicarbazide, hydroxylamine, or 2 : 4-dinitrophenylhydrazine. However, the presence of a carbonyl group was established (*a*) by its infra-red absorption spectrum (determined by the late Dr. H. P. Koch), in which a carbonyl stretching band was readily discerned at **1693** cm.$^{-1}$, (*b*) by lithium aluminium hydride reduction, which afforded the crystalline alcohol (III), which readily formed an acetate, and (*c*) by reaction with benzaldehyde in the presence of alkali, which gave the crystalline benzylidene compound (IV). The presence of one double bond was confirmed by perbenzoic acid titration of the alcohol (III), a band in the double-bond stretching frequency region also being detected in the infra-red spectrum of (I). The ketone (I) gave a negative iodoform test under the conditions given by Fuson and Tullock (*ibid.*, 1934, **56**, 1638), a result that cannot be ascribed to steric hindrance alone, for 1-acetyl*cyclo*hexene itself is very reluctant to give iodoform under these conditions.

	Ultra-violet			Infra-red (cm.$^{-1}$)	
	$\lambda_{max.}$ Å	$\epsilon_{max.}$	Ref.	C=O	C=C
1-Acetyl*cyclo*hexene	2320 3080	12 500 50	1	1663	1638
2-Acetyl-1-methyl*cyclo*hexene	2450	6 500 *	2	1686	1620
	2490	6 890 *	3		
2-Acetyl-3 : 3-dimethyl*cyclo*hexene	2320	12 000 *	4	—	—
2-Acetyl-1 : 3 : 3-trimethyl*cyclo*hexene ...	2430 3050	1 400 90	5	1693	1650

* Only principal band given.

(1) Hamlet, Henbest, and Jones, *J.*, 1951, 2652. (2) Braude *et al.*, *loc. cit.* (3) Turner and Voitle, *loc. cit.* (the infra-red data for this compound are also from this paper). (4) Chanley, *loc. cit.* (5) This paper.

Before the ultra-violet light-absorption properties of (I) could be usefully compared with those of related compounds it was necessary to show that no appreciable amounts of impurities were present in the product obtained by distillation. The homogeneity on distillation indicated that the lower-boiling (ring) $\beta\gamma$-unsaturated isomer was absent (some of the corresponding $\beta\gamma$-isomer is always formed in the preparation of 1-acetyl-2-methyl*cyclo*hexene), and further evidence for the absence of any but small quantities of this isomer was obtained by examination of the infra-red absorption spectrum, in which bands that would be shown by the trisubstituted double bond were absent. The absence of the isomeric unsaturated aldehyde (see p. 1152), which might be formed to some extent by the reversal of the direction of hydration, had already been demonstrated by the negative 2 : 4-dinitrophenylhydrazine test and was further confirmed by a negative Schiff's test. The relatively

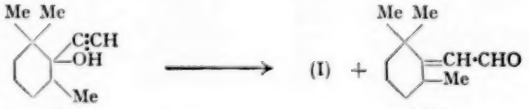
sharp melting point of the ketone (−8° to −4°) also suggested that impurities, if present, could only be there in quite small quantities.

An unsuccessful attempt was made to prepare the ketone (I) by the action of methyl-lithium on β-*cyclo*geranic acid (V). Prolonged reaction periods together with a large excess of organometallic reagent gave only unchanged (V). Conversion of an acid into the corresponding methyl ketone can be envisaged as taking place by addition of the reagent to the (potential) carbonyl group present in the initially formed lithium salt of the acid. In the present instance, the three methyl groups prevent the approach of the methyl-lithium, and thus another example is provided of the lack of carbonyl reactivity in this type of structure.

The ultra-violet absorption properties of 2-acetyl-1 : 3 : 3-trimethyl*cyclo*hexene are given in the table. The exceptionally low intensity of the main absorption band is, it is believed, unique for an αβ-unsaturated carbonyl compound, and is clearly due to steric inhibition of resonance, the three (ring) methyl groups forcing the acetyl group out of the plane of the *cyclo*hexene ring. Conjugation of the double bond with the carbonyl group is thus considerably restricted—this is also reflected in the value of the carbonyl stretching frequency in the infra-red, which approaches that of a saturated ketone (~1708 cm.$^{-1}$ in methyl ketones), and to a lesser extent by the displacement to a shorter wave-length (3050 Å) of the *R* band in the ultra-violet absorption spectrum, compared with that of 1-acetyl-*cyclo*hexene (3080 Å). The absence of appreciable amounts of βγ-isomer in the hydration product (notably that from the formic acid treatment) can also be explained by the weakness of the conjugation, the activating influence of the carbonyl group not being transmitted by the double bond to the $C_{(3)}$ carbon atom carrying the hydrogen atom(s) potentially capable of undergoing prototropic rearrangement. The similarity between the ultra-violet absorption spectra of the benzylidene compound (IV) and benzylideneacetone (see Experimental) is another manifestation of the weakness of the conjugation in this system.

Much controversy surrounds the preferred geometrical configuration of 1-acetyl*cyclo*hexenes carrying an alkyl group in the 2-position (Braude *et al.*, *loc. cit.*; Turner and Voitle, *loc. cit.*), *i.e.*, whether such compounds exist predominantly in the *s-trans-* or *s-cis*-form. Examination of models of 2-acetyl-1 : 3 : 3-trimethyl*cyclo*hexene indicates that there is less hindrance in the *s-cis*-configuration; thus the acetyl group in (I) probably occupies a position somewhat twisted out of the plane of the ring from the *s-cis*-configuration.

Another potential route to the ketone (I) was by formic acid isomerisation of (VI). This type of reaction, which gives, for example, a good yield of 1-acetyl*cyclo*hexene from 1-ethynyl*cyclo*hexanol, is known to proceed by dehydration, followed by hydration of the triple bond (Hamlet, Henbest, and Jones, *loc. cit.*). Heating the carbinol (VI) with formic acid did not give a product homogeneous on distillation,



although the main bulk exhibited light absorption similar to that of the trimethyl ketone (I), but with slightly higher intensity. The presence of a second carbonyl compound was demonstrated by a positive Schiff's test and by the ready formation of a crystalline 2 : 4-dinitrophenylhydrazone, suitable treatment of the total product affording a 9% yield (based on VI) of this derivative. This compound, which displayed the typical light absorption of those derived from αβ-unsaturated carbonyl compounds (Braude and Jones, *J.*, 1945, 498), was clearly the unsaturated aldehyde (VII), formed by 1 : 3-anionotropic shift of the hydroxyl group. Chanley (*loc. cit.*) isolated, by careful distillation, a 0·8% yield of *cyclo*hexylideneacetaldehyde from formic acid-isomerised 1-ethynyl*cyclo*hexanol, and this competing reaction proceeded to the extent of 6% with 1-ethynyl-2 : 2-dimethyl*cyclo*hexanol (Chanley, *loc. cit.*), probably owing to the greater difficulty of dehydrating the more heavily methylated ethynylcarbinols (Hamlet, Henbest, and Jones, *loc. cit.*), rearrangement of the hydroxyl group thus being relatively facilitated. Even greater yields of unsaturated

aldehydes result from certain aromatic ethynylcarbinols in which dehydration cannot take place (Clapperton and MacGregor, *J. Amer. Chem. Soc.*, 1950, **72**, 2501). The physical properties of the unreacted material recovered from the 2 : 4-dinitrophenylhydrazine treatment of isomerised (VI) agreed closely with those of 2-acetyl-1 : 3 : 3-trimethyl*cyclo*hexene, which was thus the major product of the reaction.

Experimental

(M. p.s were determined on a Kofler block and are corrected; the light-absorption data were determined in ethanol solution with a Beckman spectrophotometer unless stated otherwise.)

2-*Acetyl*-1 : 3 : 3-*trimethyl*cyclo*hexene* (I).—(a) *Boron trifluoride method.* A catalyst solution, prepared by warming together mercuric oxide (0·5 g.), trichloroacetic acid (0·08 g.), and boron trifluoride–ether (0·5 c.c.) in methanol (1·75 c.c.), was added to freshly purified 1-ethynyl-2 : 6 : 6-trimethyl*cyclo*hexene (5·2 g.) (Sobotka and Chanley, *loc. cit.*) in methanol (90 c.c.). No apparent reaction was observed on warming the reaction mixture, which was heated under reflux for one hour and then kept at room temperature overnight. Potassium carbonate (5 g.) was added, and the solution filtered. The filtrate and ether washings were evaporated under reduced pressure to remove most of the methanol, and the product was then isolated with ether. Distillation gave the homogeneous *ketone* (3·0 g.), b. p. 87—89°/16 mm., n_D^{17} 1·4778 (Found: C, 79·3; H, 10·7. $C_{11}H_{18}O$ requires C, 79·5; H, 10·9%). Light absorption: see table.

(b) *Formic acid method.* Freshly-prepared 2-ethynyl-1 : 3 : 3-trimethyl*cyclo*hexene (5·2 g.) was heated under reflux with 90% formic acid (17·2 g.) for one hour, the solution becoming brown. Isolation with ether followed by distillation gave the ketone (2·9 g.), b. p. 86·5—89°/17 mm., n_D^{16} 1·4794.

(c) *From* **1-*ethynyl*-2 : 2 : 6-*trimethyl*cyclo*hexanol*.** A solution of this alcohol [5 g.; mixture of stereoisomers obtained from 2 : 2 : 6-trimethyl*cyclo*hexanone and sodium acetylide (cf. Sobotka and Chanley, *loc. cit.*)] in 90% formic acid was heated under reflux for one hour, the solution becoming dark green. Isolation with ether gave a product (3·8 g.), b. p. 85—90°/18 mm., n_D^{22} 1·4820. Light absorption: Maximum, 2360 Å; $\varepsilon = 1950$. A portion (1 g.) of this product was added to 2 : 4-dinitrophenylhydrazine reagent [20 c.c. of a solution of the base (2 g.) in sulphuric acid (7 c.c.) and methanol (100 c.c.)], a red precipitate appearing after 20 minutes. After the mixture had been kept overnight, the precipitate was removed by filtration (see below), and the non-reacted product isolated with ether. Distillation gave almost pure trimethylketone (0·72 g.), b. p. 88—90°/20 mm., n_D^{20} 1·4775. Light absorption: Maximum, 2440 Å; $\varepsilon = 1350$.

The above derivative was purified by chromatography on alumina; elution of the main band gave **2 : 2 : 6-*trimethyl*cyclo*hexylideneacetaldehyde* 2 : 4-*dinitrophenylhydrazone*** (190 mg., 9%). Recrystallisation from ethyl acetate–chloroform gave vermilion needles, m. p. 214—215° (Found: N, 15·95. $C_{17}H_{22}O_4N_4$ requires N, 16·1%). Light absorption (in chloroform): Maxima, 2600 and 3800 Å; $\varepsilon = 16\,100$ and $31\,500$, respectively.

1-*Hydroxy*-1-2′ : 6′ : 6′-*trimethyl*cyclo*hex*-1′-*enylethane* (III).—A solution of 2-acetyl-1 : 3 : 3-trimethyl*cyclo*hexene (540 mg.) in dry ether (25 ml.) was added to a solution of lithium aluminium hydride (300 mg.) in dry ether (15 c.c.), the mixture then being heated under reflux for 3 minutes. 2N-Sulphuric acid was added to the cooled mixture, and the product was isolated with ether. Distillation gave the carbinol (430 mg., 80%), b. p. *ca.* 100°/17 mm., n_D^{17} 1·4918. This product solidified after being kept for 2 days at −8°, and after three recrystallisations from *n*-pentane (with cooling to −60°) the *carbinol* was obtained as needles, m. p. 38—38·5° (Found: C, 78·35; H, 11·9. $C_{11}H_{20}O$ requires C, 78·5; H, 11·95%).

1-*Acetoxy*-1-2′ : 6′ : 6′-*trimethyl*cyclo*hex*-1′-*enylethane*.—The carbinol (130 mg.) was dissolved in dry pyridine (10 ml.) and acetic anhydride (5 ml.), and the solution kept at 20° overnight. The excess of anhydride was decomposed by shaking the solution with water, the temperature being kept below 20° by external cooling. The product was isolated with ether; distillation then gave the *acetate* (147 mg., 90%), n_D^{19} 1·4700 (Found: C, 73·15; H, 10·4. $C_{13}H_{22}O_2$ requires C, 72·6; H, 10·6%).

Condensation of **2-*Acetyl*-1 : 3 : 3-*trimethyl*cyclo*hexene* with *Benzaldehyde*.**—The ketone (0·57 g.) and benzaldehyde (0·31 g., 0·93 mole) were dissolved in a mixture of ethanol (3 c.c.) and aqueous 2N-potassium hydroxide (1 c.c.), the solution then being warmed at 40° for 15 minutes. Isolation with ether followed by distillation gave unchanged ketone (0·23 g.) together with the crude benzylidene derivative (0·20 g.), b. p. 230—240°/0·001 mm., n_D^{21} 1·5521. This

product crystallised when kept at −8° overnight; recrystallisation from methanol–water (4 : 1) then gave the pure *benzylidene* compound (IV) as pale yellow needles (130 mg.), m. p. 49·5—51° (Found : C, 85·0; H, 8·95. $C_{18}H_{22}O$ requires C, 85·0; H, 8·7%).

Light-absorption data.

	Benzylidene derivative (IV)		Benzylideneacetone *	
	λ, Å	ε	λ, Å	ε
Max.	2230	10 500	2200	12 000
Min.	2400	1 500	2370	1 600
Max.	2930	23 100	2870	22 700

* Wilds *et al.* (*J. Amer. Chem. Soc.*, 1947, **69**, 1985).

The authors thank Professor E. R. H. Jones, F.R.S., for his interest in the work described in this and the following paper, and to Dr. B. A. Hems of Glaxo Laboratories Ltd. for generous gifts of materials. One of them (G. W.) thanks the Ministry of Education for a F.E.T.S. Grant.

THE UNIVERSITY, MANCHESTER, 13. [*Received, November 14th*, 1951.]

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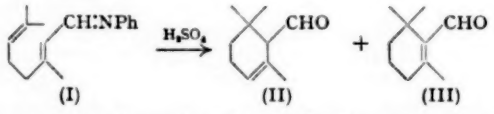
203. *Studies in the Polyene Series. Part XLI.* A New Isomerisation Product from Citral.*

By H. B. HENBEST, B. L. SHAW, and GEORGE WOODS.

A by-product isolated from the cyclisation of citral anil with 95% sulphuric acid has been shown to be 1-acetyl-4 : 4-dimethyl*cyclo*hexene, the main products being the α- and the β-*cyclo*citral.

THE most convenient method for preparing β-*cyclo*citral is that in which citral anil (I) is cyclised with sulphuric acid (D.R.-P. 123 747). This method has recently been improved by Colombi, Bosshard, Schinz, and Seidel (*Helv. Chim. Acta*, 1951, **34**, 265). Through the courtesy of Professor Schinz, who very kindly supplied us with a description of his procedure before publication, it was possible to prepare a considerable quantity of β-*cyclo*citral, required for other investigations in these laboratories.



(I) (II) (III)

The compounds known to be formed in this cyclisation are *p*-cymene, α-*cyclo*citral (II), and β-*cyclo*citral (III). These three compounds can be fairly efficiently separated by fractional distillation, but in order to procure some really pure β-*cyclo*citral, the higher-boiling fractions, consisting mostly of this isomer, were converted into the semicarbazone(s). Fractional crystallisation then gave two products, the one in larger amount proving to be β-*cyclo*citral semicarbazone (cf. Young and Linden, *J. Amer. Chem. Soc.*, 1947, **69**, 2072). The other product had a considerably higher melting point (216—218°), similar indeed to that of α-*cyclo*citral semicarbazone, but clearly differentiated from the latter by its ultra-violet light absorption—the absorption maximum at 2610 Å indicating that this new derivative had been formed from an αβ-unsaturated carbonyl compound.

Hydrolysis of the new semicarbazone afforded the parent carbonyl compound, which possesses an odour very similar to, but far more intense than, that of oil of caraway (principally carvone). Preparation of an oxime and 2 : 4-dinitrophenylhydrazone from the new ketone confirmed that it was different from carvone.

The first structures considered were those in which cyclisation had given a five-membered ring (cf. Spalding and Stevens, *ibid.*, 1949, **71**, 1687), the aldehyde group still being retained. These became untenable when it was shown that the compound was quite resis-

* Part XL, preceding paper.

tant to aerial or silver hydroxide oxidation, and gave no colour with Schiff's reagent, and that its oxime could not be dehydrated by heating it with acetic anhydride, merely being converted into the oxime acetate. Thus an αβ-unsaturated ketone rather than an aldehyde structure was indicated.

Ozonolysis of the new ketone was next investigated. Under suitable conditions a formyl or keto-acid was isolated as its crystalline 2 : 4-dinitrophenylhydrazone, but no volatile carbonyl compound was produced in the reaction. Analysis of this 2 : 4-dinitrophenylhydrazone showed that the parent compound was a C_8-acid, and this was further confirmed by analytical data obtained with the methyl ester of this derivative.

Loss of two carbon atoms on ozonolysis suggested that the partial structures (IV*a*) or (IV*b*) might be present, of which the former could be ruled out by the non-formation of acetaldehyde on ozonolysis. Confirmation of the presence of the latter partial structure was obtained by lithium aluminium hydride reduction of the ketone to the corresponding alcohol, which on treatment with osmium tetroxide gave a triol that was readily cleaved with periodic acid to give acetaldehyde together with the same C_8-formyl or -keto-acid as obtained on ozonolysis. The presence of the acetyl group in the cyclisation product could not be detected by the iodoform test (procedure of Fuson and Tullock, *ibid.*, 1934, **56**, 1638), but under these conditions, 1-acetyl*cyclo*hexene also gave a negative result.

(IV*a*) C_6H_{13}—C(=CO)—C:CHMe C_6H_{13}—C(=C)—C·COMe (IV*b*)

Comparison of the light-absorption properties of the new unsaturated ketone and its derivatives with those reported for cyclic compounds containing the partial structure (IV) revealed a very close similarity to 1-acetyl*cyclo*hexene and its derivatives (cf. Hamlet, Henbest, and Jones, *J.*, 1951, 2652). This further signified that there must be a hydrogen

(IV) $\xrightarrow{O_3}$ C_6H_{13}—C(=CO)—CO_2H + [Me·CO_2H]

$\downarrow$ $LiAlH_4$; OsO_4

C_6H_{13}—C(—OH)—C(—OH)—CH(OH)Me $\xrightarrow{IO_4'}$ CHO·Me

atom attached to the carbon atom β to the carbonyl group, for replacement of this hydrogen atom by an alkyl group markedly reduces the intensity of absorption (Braude, Jones, Koch, Richardson, Sondheimer, and Toogood, *J.*, 1949, 1890; Turner and Voitle, *J. Amer. Chem. Soc.*, 1951, **73**, 1403).

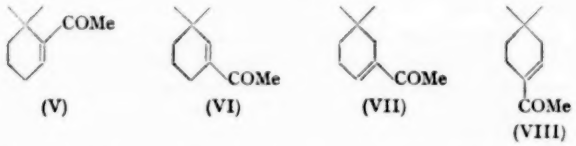
Light absorptions in ethanol.

		1-Acetyl*cyclo*hexene		Ketone	
		λ, Å	ε	λ, Å	ε
Compound	Max.	2320	12 500	2320	12 000
	Min.	2790	30	2810	30
	Max.	3080	50	3080	45
Semicarbazone	Max.	2605	24 500	2610	25 500
2 : 4-Dinitrophenylhydrazone *	Max.	2550	16 500	2550	16 800
	Min.	3120	2 000	3130	2 000
	Max.	3850	27 000	3850	27 300

* Light absorption of both in chloroform solution.

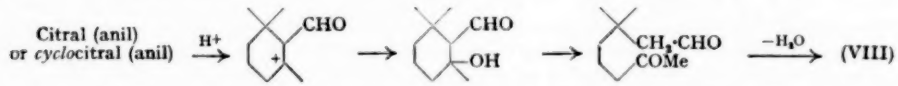
The positions of two carbon atoms now remained to be located. The ketone was not easily aromatised, for attempted dehydrogenation with sulphur (cf. Holmes, Alcock, Demianow, Robinson, Rooney, and Sunberg, *Canadian J. Res.*, 1948, **26**, *B*, 248) led to the recovery of most of the starting material. This suggested the presence of a *gem*-dimethyl grouping.

Of the four possibilities (V)—(VIII), (V) could be eliminated as this had been prepared by Chanley (*J. Amer. Chem. Soc.*, 1948, **70**, 44) and was obviously different from our



(V) (VI) (VII) (VIII)

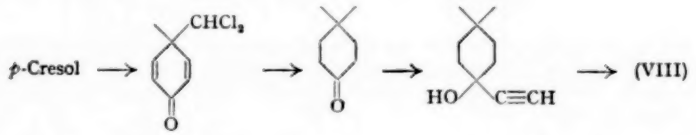
material. Consideration of the possible routes whereby (VI)—(VIII) might arise from citral, suggested that (VIII) was the only one whose formation might be accounted for by a plausible sequence of events:



Accordingly, the ketone (VIII) was synthesised from *p*-cresol by the route outlined below and shown to be identical with the product from citral.

The first stage in the isolation of the *cyclo*citral mixture involves steam-distillation of the cyclised product from dilute sulphuric acid (*i.e.*, reaction mixture diluted with ice). It seems likely that the ketone (VIII) is formed from α- and/or β-*cyclo*citral during this steam-distillation stage (by the hydration and reverse aldol changes suggested above) rather than during the cyclisation reaction. This would gain support from the observation that the yield of ketone was lower when the scale of the experiment was reduced, the time then required for the steam-distillation being correspondingly less.

This same ketone had been encountered by Haworth, Heilbron, and (W. E.) Jones (1938, unpublished work) in the course of preparing β-*cyclo*citral by the formation and cyclisation of citrylidenecyanoacetic acid. Through the courtesy of Drs. W. E. Jones and E. Haworth, who kindly provided us with a sample of their semicarbazone, a mixed m. p. determination was carried out which showed that the materials were identical. The light-absorption properties of the two semicarbazone samples were also identical, and the physical properties of the parent ketones were also in good agreement.



It is likely that a carbonyl compound isolated by Karrer and Ochsner (*Helv. Chim. Acta*, 1947, **30**, 2092) from the reaction between α- or β-*cyclo*citral (prepared from citral anil and not purified *via* crystalline derivatives) and *N*-bromosuccinimide was actually the ketone (VIII). These authors suggested a 1-formyl-2 : 6 : 6-trimethyl*cyclo*hexa-2 : 5-diene structure for their product, which cannot be correct, since a compound of this structure would absorb maximally at a wave-length >2600 Å—their reported maximum being at 2300 Å. The physical constants of the carbonyl compound and its semicarbazone given by Karrer and Ochsner agree with those of our material, and they also mention that the parent compound has an odour resembling that of kümmel (*i.e.*, caraway).

It has now been found that pure β-*cyclo*citral in ethereal solution reacts very rapidly with *N*-bromosuccinimide even at 20°, whereas the ketone (VIII) does not react appreciably under these conditions. Since β-*cyclo*citral as obtained by distillation may contain about 10% of the new ketone, it appears that the action of *N*-bromosuccinimide on this mixture is to convert the β-*cyclo*citral into non-aldehydic products, leaving the new ketone unaffected, this having then been isolated by Karrer and Ochsner as the semicarbazone.

Experimental

(M. p.s were determined on a Kofler block and are corrected; the light-absorption data were determined in ethanol solution with a Beckman spectrophotometer unless stated otherwise.)

Cyclisation of Citral Anil.—The method of Colombi, Bosshard, Schinz, and Seidel (*loc. cit.*) was employed; introduction of certain modifications enabled the scale of the experiment to be increased considerably. Sulphuric acid (1 l.) was diluted with ice (50 g.) and cooled to −20° with an acetone–solid carbon dioxide bath. The acid was stirred vigorously, the internal temperature being kept at −20° whilst the ethereal solution of citral anil (prepared from 152 g. of citral) was added during 45 minutes. The reaction mixture was stirred for a further 45 minutes at −15° and then poured on excess of ice and stream-distilled rapidly (about 40 minutes). Extraction of the distillate (*ca.* 1 l.) with ether gave a straw-coloured oil (95 g.; 64%). The combined product (285 g.) from three cyclisation experiments was fractionally distilled through a Widmer column with a totally condensing still head and a partial take off, the reflux ratio being 8 : 1 and the pressure 24 mm.; the fractions were :

No.	B. p.	n_D^{21}	Wt., g.	β-*cyclo*Citral, %	Ketone (VIII), %
1	35—89°	1·4711	23·5	—	—
2	89—96	1·4767	27·1	—	—
3	96—100	1·4810	21·7	—	—
4	100—102	1·4858	22·7	—	—
5	102—104	1·4900	19·0	71	13
6	104—106	1·4928	25·1		
7	106—107·5	1·4957	56·0	80	9
8	107·5—108	1·4964	48·0	85	7
9	108	1·4966	15·8	—	—

The percentages of β-*cyclo*citral and ketone (VIII) contained in fractions 5—8 are based on the quantities of pure semicarbazones obtained (see below); the remainder of the fractions were not investigated in this way. Fractions 2 and 3 consisted mainly of α-*cyclo*citral (pure compound has n_D^{18} 1·4744), and readily yielded α-*cyclo*citral semicarbazone, m. p. 201—203°. Light absorption: Maximum, 2320 Å; ε = 17 400.

Separation and Purification of the Semicarbazones.—Treatment of the fractions containing mostly β-*cyclo*citral with semicarbazide acetate in methanol solution gave a solid product, which on recrystallisation from slightly aqueous methanol gave 1-*acetyl*-4 : 4-*dimethyl*cyclo*hexene semicarbazone* as the most insoluble component. This compound formed plates, m. p. 216—218° (slight decomp.), from methanol (Found: C, 63·0; H, 8·95. $C_{11}H_{19}ON_3$ requires C, 63·1; H, 9·1%). Light absorption: see Table.

The β-*cyclo*citral semicarbazone could not be obtained pure by recrystallisation, the m. p. not being raised above 160—163° (Young and Linden, *loc. cit.*, give m. p. 167°). α-*cyclo*Citral semicarbazone was the suspected impurity, and the semicarbazone (m. p. 160—163°) was therefore dissolved in 0·75N-methanolic sulphuric acid at 20° to hydrolyse this impurity. Dilution with water gave pure β-*cyclo*citral semicarbazone (70% recovery), m.p. 165—168°.

Unpublished observations by Haworth, Heilbron, and Jones suggested that the following method would be more convenient. β-*cyclo*Citral (44 g.), as obtained by fractional distillation, was added to acetic acid (270 c.c.), and the solution then treated with semicarbazide hydrochloride (35 g.) in water (175 c.c.). The β-*cyclo*citral semicarbazone, which formed, was collected after 10 minutes, and recrystallised from aqueous methanol, yielding the pure derivative, m. p. 165—166°. The filtrate was treated with water and light petroleum (b. p. 40—60°), the latter extract yielding an oil that on treatment with semicarbazide acetate in methanol gave the new ketone semicarbazone, m. p. 216—218°.

1-*Acetyl*-4 : 4-*dimethyl*cyclo*hexene* (VIII).—Hydrolysis of the semicarbazone was carried out by the procedure described by Heilbron, Johnson, Jones, and Spinks (*J.*, 1942, 727); the homogeneous *ketone* produced had b. p. 102°/124 mm., n_D^{22} 1·4795 (Found: C, 78·75; H, 10·25. $C_{10}H_{16}O$ requires C, 78·9; H, 10·5%). Light absorption: see Table.

The 2 : 4-*dinitrophenylhydrazone* crystallised from methanol–ethyl acetate (1 : 1) as scarlet needles, m. p. 185·5—186° (Found: C, 57·9; H, 5·95. $C_{16}H_{20}O_4N_4$ requires C, 58·0; H, 6·0%). Light absorption: see Table.

The *oxime*, prepared in aqueous methanol solution, crystallised from methanol–water (1 : 1) as long needles, m. p. 103—104° (Found C, 71·8; H, 10·25. $C_{10}H_{17}ON$ requires C, 71·8; H, 10·2%). Light absorption: Maximum 2300 Å; ε = 17 100. Attempted dehydration (cf. theoretical section) of the oxime (320 mg.) by heating it under reflux with acetic anhydride (2 c.c.) led to a nearly quantitative yield of the *oxime acetate*, b. p. 160°/20 mm., n_D^{20} 1·4981 (Found:

C, 68·7; H, 9·2. $C_{12}H_{19}O_2N$ requires C, 68·8; H, 9·15%). Treatment of this compound with 2 : 4-dinitrophenylhydrazine reagent slowly gave the 2 : 4-dinitrophenylhydrazone of (VIII); it had m. p. 185—186°.

Ozonolysis of the Ketone (VIII).—A slow stream of ozonised oxygen (*ca.* 6% of ozone) was passed through a solution of the ketone (0·5 g.) in carbon tetrachloride (15 c.c.) for 45 minutes. The solvent was removed at room temperature under reduced pressure, and the residue subjected to steam distillation. The distillate gave no reaction with aqueous dinitrophenylhydrazine or dimedone reagents. The non-volatile residue was warmed at 60° for 20 minutes after the addition of 30% hydrogen peroxide solution (0·5 c.c.), and then treated with a 5% solution of 2 : 4-dinitrophenylhydrazine sulphate in 40% sulphuric acid, the resulting solution being kept overnight at 5°. The yellow precipitate was purified by extraction with 3% sodium hydrogen carbonate solution at 80°. Acidification of this extract gave a product which after recrystallisation from benzene–light petroleum weighed 340 mg. and had m. p. 123—134°. Further recrystallisation from benzene and then ethyl acetate gave *5-keto-3 : 3-dimethylpentane-1-carboxylic acid 2 : 4-dinitrophenylhydrazone* as small yellow needles, m. p. 135—136° (Found: C, 50·05; H, 5·5. $C_{14}H_{18}O_6N_4$ requires C, 49·7; H, 5·4%).

A solution of this derivative (88 mg.) in methanol (10 c.c.) containing 5 drops of concentrated sulphuric acid was heated under reflux for 1 hour. The product crystallised on cooling, and recrystallisation from 80% methanol then gave the 2 : 4-*dinitrophenylhydrazone* of the methyl ester as yellow needles, m. p. 82—83° (Found: C, 50·95; H, 5·85; N, 16·15. $C_{15}H_{20}O_6N_4$ requires C, 51·15; H, 5·7; N, 15·9%). Light absorption: Maxima, 2220 and 3570 Å; ε = 13 400 and 21 000; minimum, 2720 Å; ε = 1700.

Degradation of the Ketone (VIII) *by the Osmium Tetroxide–Periodic Acid Method.*—A solution of lithium aluminium hydride (100 mg.) in ether (10 c.c.) was added to one of the ketone (715 mg.) in ether (5 c.c.). The resulting solution was heated under reflux for 5 minutes, and the product was isolated with ether. Distillation gave the alcohol (608 mg.), b. p. *ca.* 110°/18 mm., n_D^{26} 1·4698, as a sweet-smelling oil.

A solution of osmium tetroxide (900 mg.) in dry ether (50 c.c) was added to one of the alcohol (513 mg.) in dry ether (10 c.c.) containing pyridine (1 c.c.). The solution immediately darkened in colour and within 3 minutes brown crystals were deposited. Filtration after 50 minutes yielded the triol–osmium–pyridine complex (1·59 g., 85%) as translucent brown needles.

For hydrolysis, this complex was dissolved in chloroform (40 c.c.) and shaken with 10% aqueous mannitol solution (100 c.c.) containing potassium hydroxide (1 g.). The reaction appeared to be complete after 10 minutes, for the initially brown chloroform layer had become colourless and the aqueous layer reddish-brown. The chloroform layer was washed with water (2 × 10 c.c.) and then rejected. The combined aqueous solution was extracted with ether for 11 hours to yield the *triol* (477 mg.) as a very viscous liquid. A portion was distilled at 100° (bath temp.; short-path still)/2 × 10^{-5} mm. (Found: C, 63·0; H, 10·5. $C_{10}H_{20}O_3$ requires C, 63·7; H, 10·6%).

(a) *Fission of the triol to give acetaldehyde.* A 10% solution of sodium metaperiodate (5 c.c.) and 2N-sulphuric acid (5 c.c.) was added to one of the triol (50 mg.) in water (30 c.c.), the mixture being shaken in nitrogen for 5 minutes. The solution was then distilled, the distillate being collected in a saturated aqueous solution of dimedone (3 c.c.). The dimedone derivative, which began to crystallise after 30 minutes, was collected after 3 days and recrystallised from ethanol–water (1 : 1) below 50°. The pure derivative (50% yield) had m. p. 139—140°, undepressed when the specimen was mixed with an authentic sample prepared from acetaldehyde (m. p. 139—140°). The dimedone derivative was also converted into its "anhydride," m. p. 177—178° undepressed when the specimen was mixed with an authentic sample, m. p. 177—178°.

(b) *Fission of the triol to the formyl acid.* The triol (350 mg.), dissolved in water (150 c.c.), was oxidised with periodic acid as before. The reaction solution was extracted with ether (5 × 15 c.c.) to give a pale yellow liquid (220 mg.), which was treated with a 5% solution of 2 : 4-dinitrophenylhydrazine in 40% sulphuric acid. After being kept at 5° for 2 days, the yellow precipitate was purified as described in the ozonolysis experiment. The product (280 mg.) had m. p. 135—136° (Found: C, 49·65; H, 5·45. Calc. for $C_{14}H_{18}O_6N_4$: C, 49·7; H, 5·4%). The m. p. was undepressed when the product was mixed with that obtained by ozonolysis. Esterification of this derivative with methanol gave the same methyl ester (m. p. and mixed m. p.) as obtained previously.

Conversion of p-*Cresol into the Ketone* (VIII).—*p*-Cresol was converted by the action of chloroform and alkali into 4-dichloromethyl-4-methyl*cyclo*hexa-2 : 5-dien-1-one by Auwers and Winternitz's method (*Ber.*, 1902, **35**, 468). This ketone was hydrogenated as described by Miller and

Adams (*J. Amer. Chem. Soc.*, 1936, **58**, 787) to 4 : 4-dimethyl*cyclo*hexanol, which was then oxidised to the corresponding ketone (cf. Auwers and Lange, *Annalen*, 1913, **401**, 315).

Dry liquid ammonia (100 c.c.) contained in a Dewar flask was saturated with acetylene; lithium (0·4 g.) was then added, and acetylene was passed in for a further 30 minutes. 4 : 4-Dimethyl*cyclo*hexanone (0·73 g.) in ether (10 c.c.) was added, and the resultant mixture was stirred for 4 hours with a slow passage of acetylene. The solvent was allowed to evaporate overnight in a slow stream of acetylene. The acetylenic alcohol was isolated with ether. Evaporation of the solvent gave the alcohol (0·77 g.), which was heated under reflux with 90% formic acid (4·5 c.c.) for 45 minutes. The product was isolated with pentane; distillation yielded the ketone (VIII) (0·47 g.), n_D^{16} 1·4794. The semicarbazone, recrystallised from methanol, had m. p. 216—219°; the oxime, recrystallised from methanol, had m. p. 103—104°; and the 2 : 4-dinitrophenylhydrazone had m. p. 183—185·5°, after recrystallisation from ethyl acetate–light petroleum (b. p. 60—80°). When the three derivatives were mixed with the corresponding compounds prepared from citral, their melting points were not depressed.

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204. *Reactions between Dialkylanilines and Hexamine in Acetic Acid and in Formic Acid.*

By J. C. DUFF and (MISS) V. I. FURNESS.

The formation of *p*-dialkylaminobenzaldehydes from dialkylanilines and hexamine in glacial acetic acid is shown to proceed by the stages shown in (I) and (II), below. When formic acid is used as the medium for the reactions, ditertiary amines of general formula *p*-$R_2N{\cdot}C_6H_4{\cdot}CH_2{\cdot}NMe_2$ are formed in addition to the aldehydes.

A GENERAL method for the preparation of *p*-dialkylaminobenzaldehydes from dialkylanilines and hexamine heated in a mixture of acetic and formic acids has been described by one of us (Duff, *J.*, 1945, 276), who suggested that the following expressed the reactions involved :

$$3R_2N{\cdot}C_6H_5 + C_6H_{12}N_4 \longrightarrow NH_3 + 3R_2N{\cdot}C_6H_4{\cdot}CH_2{\cdot}N{:}CH_2 \quad . \quad . \quad (I)$$

$$R_2N{\cdot}C_6H_4{\cdot}CH_2{\cdot}N{:}CH_2 \longrightarrow R_2N{\cdot}C_6H_4{\cdot}CH{:}N{\cdot}CH_3 \xrightarrow{H_2O} R_2N{\cdot}C_6H_4{\cdot}CHO + CH_3{\cdot}NH_2 \quad . \quad . \quad (II)$$

This mechanism corresponded to that originally put forward to explain the Sommelet reaction. Angyal and Rassack (*J.*, 1949, 2700), however, have since shown that the following steps explain the latter reaction :

$$R{\cdot}CH_2{\cdot}N{:}CH_2 + H_2O \longrightarrow R{\cdot}CH_2{\cdot}NH_2 + H{\cdot}CHO \quad . \quad . \quad . \quad (III)$$

$$R{\cdot}CH_2{\cdot}NH_2 \xrightarrow{-2H} R{\cdot}CH{:}NH \xrightarrow{H_2O} R{\cdot}CHO + NH_3 \quad . \quad . \quad . \quad (IV)$$

the hexamine acting as the dehydrogenating agent. The present authors (*J.*, 1951, 1512) found that dehydrogenation by hexamine was an essential step in the formation of *o*-hydroxyaldehydes from phenols and hexamine in a non-aqueous medium. Phenols were found to form first secondary amines of the type $HO{\cdot}X{\cdot}CH_2{\cdot}NH{\cdot}CH_2{\cdot}X{\cdot}OH$ ($H{\cdot}X{\cdot}OH$ = a phenol) followed by dehydrogenation to the Schiff's bases $HO{\cdot}X{\cdot}CH{:}N{\cdot}CH_2{\cdot}X{\cdot}OH$, which are then hydrolysed by aqueous acid.

With the above observations in mind the reactions between dialkylanilines and hexamine have been re-examined. Preliminary experiments having shown that formic acid

differs from acetic acid in yielding additional products, the reactions in both these acids have been investigated separately. In neither case has it been possible to isolate any intermediate compounds which would account for the formation of the *p*-dialkylaminobenzaldehydes, but we have found a probable example of an intermediate compound in the methylene derivative of *p*-dimethylaminobenzylamine and have been able to show that this derivative can be converted into the related aldehyde and also into the ditertiary amine, $Me_2N{\cdot}C_6H_4{\cdot}CH_2{\cdot}NMe_2$.

Reactions in Acetic Acid.—Satisfactory yields of *p*-dialkylaminobenzaldehydes were obtained by heating the dialkylanilines with hexamine in glacial acetic acid. Alcohol and aqueous formic acid, which were used in addition in the method described by Duff (*loc. cit.*), were omitted to eliminate the possibility of hydrolysis before the final treatment with dilute hydrochloric acid. No formaldehyde could be detected in the vapour arising when air was drawn through the heated reaction mixture. The absence of formaldehyde indicates that the mechanism of the reaction is not analogous to that given by Angyal and Rassack (*loc. cit.*) in scheme (III) for the Sommelet reaction.

Since the aldehyde must be formed by hydrolysis, the reaction mixture was examined for the presence of the other hydrolysis product, which could be either a primary amine or ammonia. The only primary amine detected was methylamine. Under different experimental conditions the molecular ratio of methylamine to *p*-dialkylaminobenzaldehyde was found to be always 1 : 1. The yields of the two products are shown in the table. The

Yields (in moles) from 1 *mole of dialkylaniline* *

	A		B		C	
Dialkylaniline	Aldehyde	$Me{\cdot}NH_2$	Aldehyde	$Me{\cdot}NH_2$	Aldehyde	$Me{\cdot}NH_2$
NMe_2Ph	0·18	0·185	0·305	0·305	0·145	0·145
NMeEtPh	0·26	0·26	0·23	0·23	0·05	0·05
NEt_2Ph	0·22	0·215	0·16	0·16	0·05	0·05
NPr_2Ph	0·47	0·47	0·18	0·18	0·21	0·21
NBu_2Ph	0·62	0·62	0·75	0·75	0·38	0·38
$NMePh{\cdot}CH_2Ph$	0·42	0·43	0·25	0·255	0·36	0·36
$NEtPh{\cdot}CH_2Ph$	0·61	0·62	0·46	0·46	0·355	0·355

* A = Standard conditions (see p. 1161). B = Longer heating than for A. C = Reduced proportion of hexamine compared with A.

yields recorded under B show that, although prolonged heating in most cases reduces the yields, the ratio of aldehyde to amine remains unaltered. Although a first-stage reaction as represented by

$$2R_2N{\cdot}C_6H_5 + C_6H_{12}N_4 \longrightarrow 2R_2N{\cdot}C_6H_4{\cdot}CH{:}NH + 2CH_3{\cdot}N{:}CH_2$$

can account for equivalent yields of aldehyde and methylamine, it is improbable that the 1 : 1 ratio of the two products would be maintained under conditions in which the yields are decreasing with increasing time of heating. Only hydrolysis of a single product to give both aldehyde and amine would account for the constant ratio. For this reason we consider that reactions (I) and (II) express the actual processes leading to formation of the requisite Schiff's base. These reactions include isomerisation of a methylene-azomethine type $>CH{\cdot}N{:}C< \rightleftharpoons >C{:}N{\cdot}CH<$.

Ingold and Shoppee (*J.*, 1929, 1199) examined this form of prototropy and in the case of $C_6H_5{\cdot}CH_2{\cdot}N{:}CH_2 \longrightarrow C_6H_5{\cdot}CH{:}N{\cdot}CH_3$ found that heating the methylene compound at 190° with alcoholic sodium ethoxide or at 300° with potassium hydroxide produced only about a 10% yield of benzaldehyde on subsequent hydrolysis. No reverse reaction was observed under the same conditions. Shoppee (*Nature*, 1948, **162**, 619) stated that since the isomerisation of $C_6H_5{\cdot}CH_2{\cdot}N{:}CH_2$ is only partial under drastic conditions, it is inherently improbable under mild conditions.

We have examined this isomerisation under other conditions. *N*-Methylenebenzylamine and *p*-dimethylamino-*N*-methylenebenzylamine were each heated with hexamine in acetic acid at 100° for two hours. Addition of water to the cold reaction mixtures then gave yields of 61% of benzaldehyde and 55% of *p*-dimethylaminobenzaldehyde, respectively, together with the equivalent amounts of methylamine.

When experiments were carried out with acetic acid containing 10% of water, the yield of benzaldehyde was 29%, and of *p*-dimethylaminobenzaldehyde 24%. Thus the reaction is retarded and not assisted when hydrolysis can occur, and the possibility that traces of water were favouring the reaction according to schemes (III) and (IV) is eliminated. To demonstrate that the reaction is a base-catalysed isomerisation and not a dehydrogenation, it has been examined by using other amines. With trimethylamine, yields of 40% of benzaldehyde and 46% of *p*-dimethylaminobenzaldehyde have been obtained with the formation of equivalent amounts of monomethylamine. The use of pyridine led to results of the same order.

Since isomerisation occurs readily under these conditions, it seems that a similar isomerisation could occur in the general method of preparation of the aldehydes, and that the mechanism originally suggested (*J.*, 1945, 276) and formulated in (I) and (II) is correct.

Although phenols yielded phenolic aldehydes (*J.*, 1951, 1512) *via* formation of secondary amines, it is probable that there was an initial formation of the *N*-methylenebenzylamine structure followed by further condensation with the phenol; *e.g.*,

$$HO{\cdot}C_6H_4{\cdot}CH_2{\cdot}N{:}CH_2 + C_6H_5{\cdot}OH \longrightarrow HO{\cdot}C_6H_4{\cdot}CH_2{\cdot}NH{\cdot}CH_2{\cdot}C_6H_4{\cdot}OH$$

Reactions in Formic Acid.—After dialkylanilines had been heated with hexamine in a mixture of formic acid and ethyl alcohol, addition of aqueous sodium hydroxide liberated ether-soluble oils which on distillation yielded, besides the expected aldehydes, colourless mobile liquids which were identified as a new class of ditertiary amines, *p*-dialkylaminobenzyldimethylamines, $R_2N{\cdot}C_6H_4{\cdot}CH_2{\cdot}NMe_2$. They all reacted vigorously with methyl iodide to give monoquaternary salts, $R_2N{\cdot}C_6H_4{\cdot}CH_2{\cdot}NMe_3I$. This structure was confirmed for the quaternary salts where R = Me and R = Et by thermal decomposition of the quaternary hydroxides, both of which yielded trimethylamine.

The formation of trimethylamine from the hydroxide obtained from the methiodide of *p*-dimethylaminobenzyldimethylamine suggests that the quaternary salt had been formed by addition of the methyl iodide to the aliphatic nitrogen atom, since Collie and Schryver (*J.*, 1890, **57**, 777) have shown that thermal decomposition of trimethylphenylammonium hydroxide yields dimethylaniline and methyl alcohol. The formation of trimethylamine from the hydroxide obtained from the methiodide of *p*-diethylaminobenzyldimethylamine confirms this view and proves that this hydroxide has the structure $Et_2N{\cdot}C_6H_4{\cdot}CH_2{\cdot}NMe_3{\cdot}OH$.

The ditertiary bases probably result from the initially formed methylene compounds, $R_2N{\cdot}C_6H_4{\cdot}CH_2{\cdot}N{:}CH_2$, by reduction and methylation through the combined action of formaldehyde (from hydrolysis of hexamine) and formic acid (Eschweiler, *Ber.*, 1905, **38**, 880; Clarke, Gillespie, and Weisshaus, *J. Amer. Chem. Soc.*, 1933, **55**, 4571). In support of this suggestion we have found that *N*-methylenebenzylamine and *p*-dimethylamino-*N*-methylenebenzylamine when heated with hexamine in boiling alcoholic formic acid yielded respectively benzyldimethylamine and *p*-dimethylaminobenzyldimethylamine.

Experimental

Di-*n*-propylaniline was prepared by Slotta and Franke's method (*Ber.*, 1930, **63**, 682). The other dialkylanilines were distilled from available supplies.

Reactions in Acetic Acid.—The following procedure gives the standard conditions for the results listed in Column A, of the table.

Hexamine (10 g., 0·07 mole) and glacial acetic acid (10 ml.) were heated on a boiling-water bath while a mixture of dimethylaniline (9 ml., 0·07 mole) and glacial acetic acid (20 ml.) was added dropwise during 1 hour. Heating was then continued for a further 2 hours. For the other dialkylanilines the weights used represented 0·07 mole for ethylmethyl- and diethylanilines, and 0·05 mole for di-*n*-propyl-, di-*n*-butyl-, benzylmethyl-, and benzylethyl-anilines. For the results given under B, of the table, the heating time was extended by approximately 2 hours. The results listed under C were obtained when the proportion of hexamine in the reactions was reduced by 20%, the heating time remaining the same as for the standard conditions.

Treatment of the Reaction Mixtures to determine Yields of the Aldehydes and of Methylamine.—

(a) p-*Dimethyl- and* p-*diethyl-aminobenzaldehydes.* The reaction mixtures were poured into aqueous hydrochloric acid (150 ml.; 0·5N) and set aside. The crystalline aldehydes which separated were collected and purified (see *J.*, 1945, 276). Methylamine was determined in one half of the filtrate (see below), and additional aldehyde was obtained from the other half by adding excess of sodium hydroxide solution, extracting with ether, and drying and distilling the extract. *p*-Dimethylaminobenzaldehyde (b. p. 170—175°/12 mm., m. p. and mixed m. p. 73°) and *p*-diethylaminobenzaldehyde (b. p. 168—170°/9 mm., m. p. and mixed m. p. 41°) were collected. The remainder of the extracted oils consisted mainly of unchanged dialkylaniline and the diarylmethane compounds $R_2N{\cdot}C_6H_4{\cdot}CH_2{\cdot}C_6H_4{\cdot}NR_2$ (R = Me or Et).

(b) p-*Ethylmethyl-*, p-*di*-n-*propyl-, and* p-*di*-n-*butyl-aminobenzaldehydes.* The reaction mixtures were poured into aqueous 2·5N-hydrochloric acid (150 ml.). Methylamine was determined in one half of each clear solution (see below); the other half was made alkaline, and the liberated oils were extracted with ether, dried, and distilled. *p*-Ethylmethylaminobenzaldehyde was collected at 180—184°/10 mm. and solidified, m. p. and mixed m. p. 44°. p-*Di*-n-*propylaminobenzaldehyde* was obtained as a straw-coloured oil, b. p. 180—182°/4 mm., n_D^{20} 1·5684 (Found: C, 75·7; H, 9·3; N, 6·8. $C_{13}H_{19}ON$ requires C, 76·1; H, 9·3; N, 6·8%); the *phenylhydrazone* was a fawn-coloured powder, m. p. 104° (Found: N, 14·25. $C_{19}H_{25}N_3$ requires N, 14·2%), and the p-*nitrophenylhydrazone* was dark green crystals, m. p. 164° (Found: N, 16·6. $C_{19}H_{24}O_2N_4$ requires N, 16·5%).

p-*Di*-n-*butylaminobenzaldehyde* was obtained as a colourless oil, b. p. 198—200°/3 mm., n_D^{20} 1·5852 (Found: C, 77·5; H, 10·0; N, 5·95. $C_{15}H_{23}ON$ requires C, 77·3; H, 9·9; N, 6·0%). It formed a *phenylhydrazone* as a fawn-coloured powder, m. p. 92° (Found: N, 13·1. $C_{21}H_{29}N_3$ requires N, 13·0%), and a p-*nitrophenylhydrazone* as dark red crystals, m. p. 133° (Found: N, 15·4. $C_{21}H_{28}O_2N_4$ requires N, 15·2%).

(c) p-*Benzylmethyl- and* p-*benzylethyl-aminobenzaldehydes.* The reaction mixture was poured into aqueous hydrochloric acid (100 ml.; approx. 5N). Methylamine was determined (see below) in one half of the clear solution; the other half was made alkaline and the liberated oil extracted with ether. After removal of the ether by distillation, the aldehyde in the oil was collected as the *p*-nitrophenylhydrazone; the derivative of *p*-benzylmethylaminobenzaldehyde had m. p. 179°, and that of *p*-benzylethylaminobenzaldehyde, m. p. 164°, in agreement with those given by Duff (*J.*, 1945, 276).

Methylamine. The reserved solution from each preparation was made alkaline with sodium hydroxide, and the liberated volatile amines were distilled and collected in excess of hydrochloric acid. This solution was evaporated to dryness, and the mixed hydrochlorides were extracted first with chloroform to remove di- and tri-methylamine salts and then with *n*-butyl alcohol at 100° to dissolve methylamine hydrochloride. The amines were then determined by distilling them into standard acid. In no case was more than 0·01 mole of mixed di- and tri-methylamines found, and in general the amount was much less.

Reactions of N-*Methylenebenzylamine and* p-*Dimethylamino*-N-*methylenebenzylamine.*—*N*-Methylenebenzylamine, m. p. 48°, was prepared from benzylamine and formaldehyde (Ingold and Shoppee, *J.*, 1929, 1199). *p*-Dimethylaminobenzylamine, b. p. 150°/14 mm., was prepared by reduction of *p*-dimethylaminobenzaldoxime with 3% sodium amalgam (Shoppee, *J.*, 1931, 1225) and then stirred with excess of 40% formaldehyde solution. The aqueous layer was removed from the lower viscous liquid, and the latter dried *in vacuo* over concentrated sulphuric acid and finally washed with ethyl alcohol. The product was p-*dimethylamino*-N-*methylenebenzylamine*, a white powder, m. p. 97° (Found: C, 74·3; H, 8·7; N, 17·2. $C_{10}H_{14}N_2$ requires C, 74·1; H, 8·6; N, 17·3%). *N*-Methylenebenzylamine (1 g., 0·0084 mole) and hexamine (1 g.) were heated in glacial acetic acid (3 ml.) on a steam-bath for 2 hours. No formaldehyde could be detected in the vapour carried off by a current of dry air passing through the solution during the heating period. The reaction mixture was cooled, and water added. The odour of benzaldehyde was noticed immediately. Methylamine was determined in one half of the aqueous solution by the method described above, and benzaldehyde in the other half by formation of the 2 : 4-dinitrophenylhydrazone following Shoppee's method (*J.*, 1931, 1225). For the whole batch the amount of methylamine was 0·16 g. (0·0052 mole) and the amount of benzaldehyde was 0·54 g. (0·0051 mole). *p*-Dimethylamino-*N*-methylenebenzylamine (1 g., 0·0061 mole), submitted to the same treatment as for *N*-methylenebenzylamine, gave methylamine (0·105 g., 0·034 mole) and *p*-dimethylaminobenzaldehyde (0·49 g., 0·0033 mole); determined as the *p*-nitrophenylhydrazone.

Use of trimethylamine in place of hexamine (in the same molar proportions) in the above isomerisation experiments resulted in yields of 0·0036 mole of benzaldehyde and 0·0028 mole

of *p*-dimethylaminobenzaldehyde. Use of pyridine similarly gave yields of 0·0034 mole of benzaldehyde and 0·0025 mole of *p*-dimethylaminobenzaldehyde.

Reactions in Formic Acid.—Hexamine (40 g.) and ethyl alcohol (40 ml.) were heated on a steam-bath while a mixture of dimethylaniline (30 ml., 0·24 mole) and formic acid (100 ml., 85%) was added dropwise during 3 hours. Heating was continued for a further 2 hours. The reaction mixture was then cooled, diluted with water (100 ml.), and made alkaline with sodium hydroxide solution. The oil which separated was extracted with ether, dried, and distilled. The fraction, b. p. 135—136°/10 mm., was p-*dimethylaminobenzyldimethylamine* (6·4 g.), n_D^{20} 1·5422 (Found: C, 74·6; H, 9·9; N, 15·8. $C_{11}H_{18}N_2$ requires C, 74·2; H, 10·1; N, 15·7%). A *methiodide*, formed immediately on addition of methyl iodide to an ethereal solution of the amine, was a microcrystalline powder, m. p. >250° (Found: N, 8·7; I, 39·6. $C_{12}H_{21}N_2I$ requires N, 8·75; I, 39·7%). A *monopicrate* of the ditertiary amine was obtained as orange-yellow crystals, m. p. 143° (Found, by use of titanous sulphate: NO_2, 34·0. $C_{11}H_{18}N_2,C_6H_3O_7N_3$ requires NO_2, 33·9%), and a *dipicrate* as bright yellow crystals, m. p. 163° (Found: NO_2, 43·7. $C_{11}H_{18}N_2,2C_6H_3O_7N_3$ requires NO_2, 43·4%).

The same method and the same molal proportions being used, ethylmethylaniline yielded p-*ethylmethylaminobenzyldimethylamine* (0·4 g.), b. p. 126—127°/5 mm., n_D^{20} 1·5399 (Found: C, 74·9; H, 10·6; N, 14·6. $C_{12}H_{20}N_2$ requires C, 75·0; H, 10·4; N, 14·6%). This gave a *methiodide* as a crystalline powder, m. p. 139—140° (decomp.) (Found: N, 8·6; I, 38·0. $C_{13}H_{23}N_2I$ requires N, 8·4; I, 38·0%). A *monopicrate* was obtained as orange-yellow crystals, m. p. 93° (Found: NO_2, 32·9. $C_{12}H_{20}N_2,C_6H_3O_7N_3$ requires NO_2, 32·8%), and a yellow crystalline *dipicrate*, m. p. 158° (Found: NO_2, 42·5. $C_{12}H_{20}N_2,2C_6H_3O_7N_3$ requires NO_2, 42·5%). Similarly, diethylaniline yielded p-*diethylaminobenzyldimethylamine* (4·4 g.), b. p. 150—151°/8 mm., n_D^{20} 1·5425 (Found: C, 75·6; H, 10·7; N, 13·6. $C_{13}H_{22}N_2$ requires C, 75·7; H, 10·7; N, 13·6%). This formed a *methiodide*, a microcrystalline powder, m. p. 146° (Found: N, 80·5; I, 36·5. $C_{14}H_{25}N_2I$ requires N, 8·05; I, 36·5%), a *monopicrate*, yellow crystals, m. p. 105° (Found: NO_2, 31·8. $C_{13}H_{22}N_2,C_6H_3O_7N_3$ requires NO_2, 31·7%), and a *dipicrate*, yellow crystals, m. p. 151° (Found: NO_2, 42·1. $C_{13}H_{22}N_2,2C_6H_3O_7N_3$ requires NO_2, 41·6%).

For the remaining dialkylanilines the best yields of the ditertiary amines were obtained by reducing the proportion of the dialkylaniline in the above preparation method from 0·24 to 0·12 mole. Di-*n*-propylaniline yielded p-*di*-n-*propylaminobenzyldimethylamine* (0·1 g.), b. p. 138—139°/4 mm., n_D^{20} 1·5130 (Found: C, 76·7; H, 10·9; N, 11·9. $C_{15}H_{26}N_2$ requires C, 76·9; H, 11·1; N, 12·0%). It formed a *methiodide*, a microcrystalline powder, m. p. 147° (Found: N, 7·7; I, 33·9. $C_{16}H_{29}N_2I$ requires N, 7·4; I, 33·8%), and a yellow crystalline *dipicrate*, m. p. 140° (Found: NO_2, 39·9. $C_{15}H_{26}N_2,2C_6H_3O_7N_3$ requires NO_2, 39·9%).

Di-*n*-butylaniline yielded p-*di*-n-*butylaminobenzyldimethylamine* (0·4 g.), b. p. 160—161°/4 mm., n_D^{20} 1·5261 (Found: C, 78·1; H, 11·6; N, 10·4. $C_{17}H_{30}N_2$ requires C, 77·9; H, 11·4; N, 10·7%). It yielded a *methiodide* as a microcrystalline powder, m. p. 135—136° (Found: N, 7·0; I, 31·6. $C_{18}H_{33}N_2I$ requires N, 6·9; I, 31·4%), and a yellow crystalline *dipicrate*, m. p. 114° (decomp.) (Found: NO_2, 38·1. $C_{17}H_{30}N_2,2C_6H_3O_7N_3$ requires NO_2, 38·3%). Benzylmethylaniline yielded p-*benzylmethylaminobenzyldimethylamine* (4·2 g.), b. p. 215—216°/8 mm., n_D^{20} 1·6015 (Found: C, 79·9; H, 8·5; N, 11·2. $C_{17}H_{22}N_2$ requires C, 80·3; H, 8·7; N, 11·0%). It formed a *methiodide* as a microcrystalline powder, m. p. 140—144° (decomp.) (Found: N, 7·1; I, 31·8. $C_{18}H_{25}N_2I$ requires N, 7·1; I, 32·1%), a yellow crystalline *monopicrate*, m. p. 140° (Found: NO_2, 28·4. $C_{17}H_{22}N_2,C_6H_3O_7N_3$ requires NO_2, 28·5%), and a yellow crystalline *dipicrate*, m. p. 163° (decomp.) (Found: NO_2, 38·6. $C_{17}H_{22}N_2,2C_6H_3O_7N_3$ requires NO_2, 38·7%). Benzylethylaniline yielded p-*benzylethylaminobenzyldimethylamine* (2·9 g.), b. p. 210—211°/3 mm., n_D^{20} 1·5943 (Found: C, 80·6; H, 9·3; N, 10·2. $C_{18}H_{24}N_2$ requires C, 80·6; H, 9·0; N, 10·4%). It formed a *methiodide* as a microcrystalline powder, m. p. 157° (decomp.) (Found: N, 6·9; I, 30·95. $C_{19}H_{27}N_2I$ requires N, 6·8; I, 31·0%), and a yellow crystalline *monopicrate*, m. p. 110° (Found: NO_2, 27·9. $C_{18}H_{24}N_2,C_6H_3O_7N_3$ requires NO_2, 27·7%).

Examination of the Quaternary Salts.—The methiodides formed by *p*-dimethyl- and *p*-diethyl-aminobenzyldimethylamine were shaken in water with precipitated silver oxide. The filtered solutions of the quaternary hydroxides were evaporated *in vacuo*, the crystalline bases remaining were decomposed by heating, and the alkaline vapours were absorbed in hydrochloric acid. Evaporation of the acid solutions in both cases yielded trimethylamine hydrochloride, m. p. 277—278° [platinichloride, m. p. 242° (Found: Pt, 37·2. Calc. for $2C_3H_9N,H_2PtCl_6$: Pt, 37·1%)].

*Reactions of Methylenebenzylamine and Methylene-*p*-dimethylaminobenzylamine.*—*N*-Methyl-

enebenzylamine (2 g.), hexamine (2 g.), and ethyl alcohol (2 ml.) were heated on a steam-bath while formic acid (6 ml., 85%) was added dropwise during an hour. Heating was continued for 2 hours. The reaction mixture was diluted with water, made alkaline with sodium hydroxide solution, and extracted with ether. The dried ethereal solution was distilled. The oil collected at 72°/10 mm. was benzyldimethylamine but contained a small proportion of benzaldehyde. The amine was purified by dissolving it in hydrochloric acid and removing the aldehyde by ether extraction; 0·7 g. of benzyldimethylamine was recovered from the acid solution and identified as methiodide, m. p. 179—180° (Found : N, 5·1. Calc. for $C_{10}H_{16}NI$: N, 5·05%). *p*-Dimethylamino-*N*-methylenebenzylamine (1 g.) was subjected to the above treatment and yielded *p*-dimethylaminobenzyldimethylamine (0·62 g.), b. p. 130—132°/10 mm. It yielded the same derivatives as those already recorded in its preparation from dimethylaniline.

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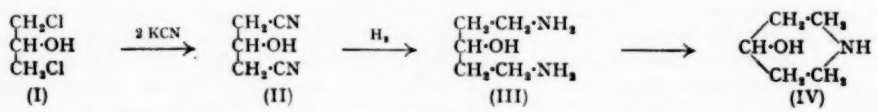
205. *Syntheses in the Piperidine Series. Part I. A Facile Synthesis of Piperidin-4-ol, and the Preparation of Related Compounds.*

By K. BOWDEN and P. N. GREEN.

Contrary to earlier work, 1 : 3-dichloropropan-2-ol reacts with potassium cyanide to give 1 : 3-dicyanopropan-2-ol. This, on catalytic hydrogenation, yields piperidin-4-ol, making an easy synthesis of this compound available. Even when the hydrogenation is carried out in the presence of liquid ammonia the formation of piperidin-4-ol predominates over the formation of the open-chain diamine, 1 : 5-diaminopentan-3-ol. 4-Hydroxypiperidinium bromide with phosphorus tribromide gives 4-bromopiperidinium bromide which may be readily converted into 1-benzoyl-4-bromopiperidine. 1-Acetylpiperidin-4-ol may be prepared by the action of either acetamide or methyl acetate on piperidin-4-ol. 1-Methylpiperidin-4-ol is readily obtained by the reductive methylation of piperidin-4-ol with formaldehyde and formic acid. 1-Methylpiperid-4-one can be prepared from bis-2-chloroethyl ketone and methylamine.

A PROGRAMME of synthetical work, which will be reported later, aimed at the preparation of potential chemotherapeutic agents required piperidin-4-ol and related compounds as intermediates. The recorded methods of synthesising piperidin-4-ol generally required difficultly accessible starting materials and, besides being time-consuming, gave low overall yields (Koenigs and Neumann, *Ber.*, 1915, **48**, 956; McElvain and McMahon, *J. Amer. Chem. Soc.*, 1949, **71**, 901). It therefore seemed worth while to investigate the following route which would involve only three stages and would require as starting material easily accessible 1 : 3-dichloropropan-2-ol (I) :



(I) (II) (III) (IV)

Simpson (*Annalen*, 1865, **133**, 75) unsuccessfully attempted to prepare 1 : 3-dicyanopropan-2-ol (II) from (I) and potassium cyanide; Morgensen and Zerner (*Monatsh.*, 1910, **31**, 778) claimed the isolation of (II), describing it as an amorphous solid unstable to distillation, but this was later shown to be incorrect by Lespieau (*Compt. rend.*, 1923, **176**, 754) and Legrand (*Bull. Soc. chim. Belg.*, 1944, **53**, 166), who prepared the compound from 1-chloro-3-cyanopropan-2-ol and found it to be a stable liquid.

Contrary to Simpson (*loc. cit.*) we found that (II) can be prepared from (I) and sodium

cyanide. The use of water as solvent gave higher yields than when alcohol was employed, and sodium cyanide was superior to potassium cyanide for the reaction. Some commercial samples of (I) were unsatisfactory as starting materials even after careful distillation, but consistent results were obtained with (I) prepared by the usual method from 3-chloropropylene oxide and hydrogen chloride (Hill and Fischer, *J. Amer. Chem. Soc.*, 1922, **44**, 2584).

The preparation of 1 : 5-diaminopentan-3-ol (III) by reduction of (II) with sodium and alcohol was claimed by Morgensen and Zerner (*loc. cit.*), who characterized their product as a picrate, but in view of the doubtful nature of their starting material, the lack of analytical data, and the melting point of the derivative, their results must be accepted with some reserve. We found that reduction of (II) with sodium and either ethyl or *n*-butyl alcohol gave indifferent yields of (III), and difficulties were experienced in the isolation of the product.

Catalytic reduction of cyanides is frequently a suitable method of preparing amines and the presence of ammonia usually suppresses the formation of secondary amines (Schwoegler and Adkins, *J. Amer. Chem. Soc.*, 1939, **61**, 3501; Huber, *ibid.*, 1944, **66**, 876; Biggs and Bishop, *Org. Synth.*, 1947, **27**, 18). The cyanide (II) was therefore catalytically hydrogenated in alcoholic ammonia and also in anhydrous ammonia. Although the products from these reactions contained some of the open-chain diamine (III), in all cases piperidin-4-ol (IV) predominated. Hydrogenation of (II) in the absence of ammonia further increased the yield of (IV). Rapid hydrogenation of (II) gave the best yield of (IV), slow hydrogenation producing some high-molecular weight material, formed probably by the polymerization of intermediate imine. Thus there was available a two-stage synthesis of piperidin-4-ol requiring only simple starting materials.

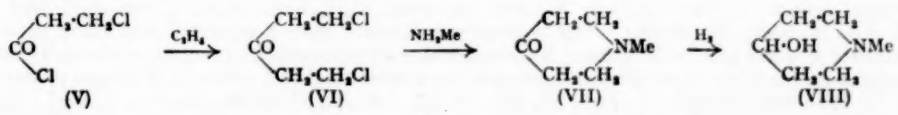
Many simple salts of piperidin-4-ol are hygroscopic, but we found that the sulphate tetrahydrate, m. p. 66—88°, is non-hygroscopic; it is converted into the anhydrous sulphate, m. p. 272—274°, when dried in a vacuum desiccator, and in air reverts to the tetrahydrate. The hydrated salt, being soluble in hot 95% alcohol, is useful for separating (IV) from (III), the sulphate of which is insoluble in the same solvent.

4-Bromopiperidine was prepared by Koenigs and Neumann (*loc. cit.*) by the action of fuming hydrobromic acid on (IV) in a sealed tube. We were unable to obtain the yield quoted, and the product was difficult to decolourize. We found that the compound could be readily prepared from phosphorus tribromide and the hydrobromide of (IV), and that the product was easily purified.

Leffler and Adams's acylation method (*J. Amer. Chem. Soc.*, 1937, **59**, 2256) was used for the preparation of 1-benzoyl-4-bromopiperidine but failed with (IV). The 1-acetyl derivative of (IV) was readily obtained from (IV) by the action of (*a*) acetamide in boiling *cyclo*hexanol or (*b*) methyl acetate.

The preparation of 1-methylpiperidin-4-ol (VIII) has been attended in the past by the same difficulties as are encountered in the preparation of (IV). Reductive methylation of (IV) with formaldehyde and formic acid gave excellent yields of (VIII) (cf. Clarke, Gillespie, and Weisshaus, *J. Amer. Chem. Soc.*, 1933, **55**, 4571).

The preparation of (VIII) from 1-methylpiperid-4-one (VII) has already been reported (McElvain and Rorig, *J. Amer. Chem. Soc.*, 1948, **70**, 1826). The following route to (VIII) was therefore explored:



The formation of (VI) from (V) has been described elsewhere (B.P. 459 537), but we found that to obtain good yields it was necessary to add the ethylene and aluminium chloride simultaneously to (V). During the course of this work, Cardwell and McQuillin (*J.*, 1949, 708) described the use of nitromethane as solvent in this reaction.

By the reaction of methylamine with (VI) in aqueous sodium carbonate (VII) was

formed, but in view of the ease of preparation of (VIII) from (IV) this route was not investigated further. The simple salts of (VIII), with the exception of the picrate, were hygroscopic.

Experimental

1 : 3-*Dicyanopropan*-2-*ol* (II).—To sodium cyanide (54 g.) in warm water (60 ml.) was added 1 : 3-dichloropropan-2-ol (65 g.) in one portion, and whilst vigorously stirred, the mixture was warmed to 50°. The temperature was held at 50—55° for 40 minutes by ice-water cooling; the mixture was then allowed to cool and was stirred overnight. After neutralisation (litmus) with 5N-hydrochloric acid, the mixture was filtered and the residue and filtrates extracted with ethyl acetate (4 × 50 ml.). The extracts were dried (Na_2SO_4) and distilled under reduced pressure, giving 1-chloro-3-cyanopropan-2-ol (6·3 g.), b. p. 85—105°/0·01—0·03 mm., followed by 1 : 3-dicyanopropan-2-ol. The latter, a pale yellow, viscous oil (23·3 g.), b. p. 145—155°/0·02—0·05 mm., was characterized by conversion into 2-bromo-1 : 3-dicyanopropane, m. p. 91° (from water) (Lespieau, *loc. cit.*, gives m. p. 87—88°); and into 2-bromo-1 : 3-dicyanopropane bromohydrate which formed long needles, m. p. 228° (from water) (Lespieau, *loc. cit.*, gives m. p. 230°). No increase in yield was obtained when 1 : 3-dibromopropan-2-ol replaced the dichloro-compound.

Piperidin-4-*ol* (IV).—1 : 3-Dicyanopropan-2-ol (45 g.) in ethanol (400 ml.; 95%) was hydrogenated in a magnetically stirred autoclave (750 ml. capacity) in the presence of Raney nickel (10 g.) at 50° and 50 atmospheres. Hydrogenation was complete in 2 hours. The solution was then filtered and distilled under reduced pressure to give (IV) (17·6 g.) as a colourless, highly viscous oil, b. p. 110—115°/10 mm., which crystallized in the receiver. The platinichloride, prepared in alcoholic solution, had m. p. 195° (decomp.) [Koenigs and Neumann, *loc cit.*, give m. p. 184—187° (decomp.)] [Found : C, 19·75; H, 4·0. Calc. for $(C_5H_{11}ON)_2PtCl_6$: C, 19·6; H, 3·9%]. The crude hydrogenation product, on neutralization with dilute sulphuric acid and evaporation to dryness, gave a solid which was treated with hot 95% ethanol. From the filtrates 4-*hydroxypiperidinium sulphate tetrahydrate* crystallized as needles, m. p. 66—68° (Found : C, 32·4; H, 8·2; S, 8·4. $2C_5H_{11}ON,H_2SO_4,4H_2O$ requires C, 32·3; H, 8·6; S, 8·6%). When kept in a vacuum desiccator this compound changed into the anhydrous sulphate, m. p. 272—274° (Koenigs and Neumann, *loc. cit.*, give m. p. 263—266°) (Found : C, 39·8; H, 8·2; S, 11·0. Calc. for $2C_5H_{11}ON,H_2SO_4$: C, 40·0; H, 8·0; S, 10·7%). The ethanol-insoluble material was dissolved in a minimum of water, and added to an excess of saturated sodium picrate in water. Yellow needles separated and were crystallized from hot water giving 1 : 5-*diaminopentan*-3-*ol dipicrate*, m. p. 238° (decomp.) (Found : C, 35·8; H, 3·6; N, 19·4. $C_5H_{14}ON_2,2C_6H_3O_7N_3$ requires C, 35·5; H, 3·5; N, 19·4%) [Morgensen and Zerner, *loc. cit.*, reported m. p. 272° (decomp.) for this compound, but gave no analytical figures].

4-*Bromopiperidinium Bromide*.—Piperidin-4-ol (3 g.) was dissolved in aqueous hydrobromic acid (10 g.; 47%) and the solution concentrated to dryness under reduced pressure. The residue was dissolved in hot ethanol (10 ml.), and the solvent then removed under reduced pressure to give a crystalline hydrobromide, m. p. 104—106°. Phosphorus tribromide (5 g.) was added and the mixture refluxed for 10 minutes. When the mixture was cold, excess of phosphorus tribromide was removed under reduced pressure and the residue was extracted three times with sodium-dried ether, and then with three lots of hot absolute alcohol, from which crystals, m. p. 192—193° (decomp.), were deposited. These were recrystallized from *n*-butanol, giving 4-bromopiperidinium bromide (2·8 g.), m. p. 192—193° (decomp.) (cf. Koenigs and Neumann, *loc. cit.*). By the addition of an aqueous solution of this salt to a saturated solution of sodium picrate in water the *picrate* was obtained as yellow prisms, m. p. 162—163° (from hot water) (Found : C, 33·8; H, 3·3; N, 14·0; Br, 20·4. $C_5H_{10}NBr,C_6H_3O_7N_3$ requires C, 33·6; H, 3·3; N, 14·2; Br, 20·3%). The *sulphate* was prepared from a saturated solution of silver sulphate in water and the bromide. After removal of silver bromide, the sulphate was obtained by evaporation followed by recrystallization of the residue from 95% ethanol; it formed prisms, m. p. 163—164° (Found : C, 28·5; H, 5·3; N, 6·3. $2C_5H_{10}NBr,H_2SO_4$ requires C, 28·2; H, 5·2; N, 6·6%).

1-*Benzoyl*-4-*bromopiperidine*.—To a solution of benzoyl chloride (1·54 g.) in benzene (5 ml.) was added, with stirring, a solution of 4-bromopiperidinium bromide (2·45 g.) in water (15 ml.); followed by one of sodium carbonate (1·27 g.) in water (12·7 ml.), added dropwise, at 5°. After 2 hours' stirring, the mixture was extracted three times with benzene, and the extracts dried (Na_2SO_4). The solvent was removed under reduced pressure leaving an oil which slowly

solidified. Crystallization from light petroleum (b. p. 60—80°) gave 1-*benzoyl*-4-*bromopiperidine* as prisms (2 g.), m. p. 67—69° (Found: C, 53·6; H, 5·1; N, 5·1. $C_{12}H_{14}ONBr$ requires C, 53·7; H, 5·3; N, 5·2%).

1-*Acetylpiperidin*-4-*ol*.—(*a*) Piperidin-4-ol (5 g.) in methyl acetate (6 ml.) was refluxed for 78 hours, and the mixture then distilled under reduced pressure to give unchanged piperidin-4-ol (1·5 g.), followed by an oil, b. p. 176—178°/10 mm., which crystallized in the receiver. This product was recrystallized giving 1-*acetylpiperidin*-4-*ol* (3·0 g.) as hygroscopic prisms, m. p. 66—67° (Found: C, 58·3; H, 9·3; N, 9·7. $C_7H_{13}O_2N$ requires C, 58·7; H, 9·2; N, 9·8%).

(*b*) Piperidin-4-ol (2·5 g.), acetamide (1·5 g.), and *cyclo*hexanol (5 g.) were refluxed for 6 hours in an apparatus equipped with a soda-lime tube. The resulting mixture was distilled under reduced pressure giving 1-acetylpiperidin-4-ol (1·5 g.), b. p. 180—182°/11 mm., identical with material obtained by method (*a*). The compound is readily soluble in water and insoluble in dry ether.

Di-2-*chloroethyl Ketone*.—Into β-chloropropionyl chloride (170 g.) was passed a steady stream of ethylene whilst powdered aluminium chloride (187 g.) was added portionwise. During the addition, which took 3½ hours, the temperature was kept at 20—25° and the ethylene was passed in as fast as it could be absorbed by the mixture. After addition of the aluminium chloride was complete, ethylene was passed in at the same temperature for 1 hour, whereupon no further absorption took place. Next morning the mixture was poured on a mixture of ice and dilute hydrochloric acid, whereupon a heavy oil separated. The mixture was extracted with ether, and the ethereal solution washed twice with water, dried (Na_2SO_4), and distilled through a fractionating column, giving di-2-chloroethyl ketone (89 g.), b. p. 79—89°/10 mm. (Caldwell and McQuillin, *loc. cit.*, give b. p. 78°/6 mm.—88°/10 mm.).

1-*Methylpiperid*-4-*one*.—A solution of sodium carbonate (6·3 g.) in water (70 ml.) was added dropwise during 45 minutes to a solution of di-2-chloroethyl ketone (4·65 g.) in absolute alcohol (30 ml.) at room temperature. Simultaneously methylamine gas was introduced into the mixture. When the addition was complete the mixture was refluxed for 1 hour. Next morning, after being evaporated to half its volume, the solution was treated with potassium hydroxide, and a dark oil separated. The mixture was extracted well with ether, the ethereal solution dried (Na_2SO_4), and the solvent evaporated giving methylpiperid-4-one (0·75 g.), b. p. 55—59°/14 mm. The product reacted with benzaldehyde to give 3 : 5-dibenzylidene-1-methylpiperid-4-one, m. p. 117° (cf. Howton, *J. Org. Chem.*, 1945, **10**, 279).

1-*Methylpiperidin*-4-*ol*.—To a cooled solution of piperidin-4-ol (5 g.) in 90% formic acid solution (8 g.) was added 40% aqueous formaldehyde solution (5 g.). The mixture was heated on the steam-bath for 8 hours. Next morning concentrated hydrochloric acid (10 ml.) was added, and the mixture refluxed for 5 minutes and then evaporated under reduced pressure, giving an oil. The oil was dissolved in water (5 ml.), and 50% aqueous potassium hydroxide (10 ml.) added, giving a brown oil. The mixture was extracted well with benzene and the extract dried (Na_2SO_4) and distilled, giving 1-methylpiperidin-4-ol (4·3 g.), b. p. 95—96°/10 mm. The *methiodide* crystallized from ethanol as prisms, m. p. 327° (decomp.) (Found: C, 32·9; H, 6·4; N, 5·3; I, 49·3. $C_6H_{13}ON,CH_3I$ requires C, 32·7; H, 6·3; N, 5·4; I, 49·4%).

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206. *Investigations of Aromatic Sulphides and Sulphones. Ultra-violet Absorption Spectra of Some Diaryl Sulphides.*

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The ultra-violet absorption spectra of a considerable number of mono- and di-substituted derivatives of diphenyl sulphide have been investigated. The substituents were CH_3, Cl, Br, I, NH_2, NHAc, and NO_2; and the spectra of some of the amino-compounds have been measured also in aqueous hydrochloric acid solution. The spectra are analysed in terms of chromophores; and the polar influence of substituents, and the steric effect of *ortho*-substituents, are discussed. The two bands of diphenyl sulphide are assigned to different upper electronic states, arising essentially from the excitation of different chromophores, which it is allowable to consider separately, because the non-planar nature of the molecule permits sulphur to be strongly conjugated only with one ring at a time, and does not allow an effective through-conjugation including both rings. The spectra of the derivatives receive a consistent interpretation of this basis. Methyl and halogen substituents make only minor spectral modifications, but NX_2 and NO_2 have large spectral effects, which can be understood on the basis that functional conjugation, originating in NX_2, extends through the directly attached benzene ring only, while conjugation arising from NO_2 extends at least as far as this, though from a *p*-nitro-group it can also include the sulphur atom. The steric inhibition of conjugation of *o*-NO_2 and -NHAc groups with the aromatic ring can be seen in the spectra of a number of the examples.

Our work on conjugation and hyperconjugation (Mangini, *Atti Accad. Lincei*, 1949, **7**, 321) has been concerned with the electronic absorption spectra of aryl sulphides, sulphoxides, and sulphones, and with the effect thereon of substituents. The mode of involvement of sulphur in the aromatic chromophores is of special interest, since the rings of diphenyl sulphide are not coplanar (Toussaint, *Bull. Soc. chim. Belg.*, 1948, **54**, 319). This paper deals particularly with the ultra-violet absorption spectra of diphenyl sulphide, and of its derivatives having CH_3, Hal, NX_2, and NO_2 as substituents.

Experimental.—Carefully purified materials, prepared as indicated in the tables, were spectrally examined with the Beckman quartz instrument D.U., and occasionally with a Zeiss spectrograph, hydrogen and tungsten lamps being employed as light sources. Spectra were taken in solution, of concentration 1 in 10^5, in 95% ethanol or 2N-aqueous hydrochloric acid, readings being normally 1—2 mμ apart. In the tables, spectral positions and intensities of characteristic points are expressed in mμ and log ε/mole, respectively. The relatively lower accuracy of flat maxima and shoulders is indicated by parentheses and asterisks, respectively.

Discussion

(1) *Diphenyl Sulphide* (Table 1, No. 1, Fig. 1).—This spectrum has been recorded by Fox and Pope (*J.*, 1913, **103**, 1264) and by Chaix (*Bull. Soc. chim.*, 1933, **53**, 700), and during the course of our work, by the other authors quoted below [Robertson and Matsen (*J. Amer. Chem. Soc.*, 1950, **72**, 5250) give curves but not numerical data for band maxima]:

	mμ	log ε	mμ	log ε
Fehnel and Carmack [1]	250	4·08	277 [3]	3·76
Koch [2]	250	4·08	274	3·76
Present authors	250	4·08	274	3·75

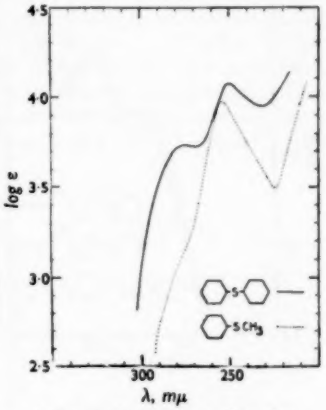
[1] *J. Amer. Chem. Soc.*, 1949, **71**, 84.
[2] *J.*, 1949, 387.
[3] The present authors obtained 277 mμ for this band with partly purified material, but the value shifted to and remained at 274 mμ after continued purification.

The spectrum is dominated by two bands, the stronger at 250 mμ and the weaker at 274 mμ, and different descriptions have been offered of their electronic origin. Fehnel

and Carmack deduce conjugation between the sulphur atom and the rings. Koch regards the bands as arising from transitions of the whole molecule, distinguished by the directions of the oscillating electric vectors. Robertson and Matsen think of the molecule essentially as a monosubstituted benzene, the PhS substituent perturbing the benzene system.

Apart from the circumstance that the bands obviously do not represent either a vibrational structure in, or a resonance doubling of, a single electronic transition, we have had in mind the analogy of the spectrum with those of diaryl and alkyl aryl ethers (Doub and Vandenbelt, *J. Amer. Chem. Soc.*, 1947, **69**, 2716; Robertson, Sceriff, and Matsen, *ibid.*, 1950, **72**, 1545), and specially with those of alkyl phenyl sulphides. The latter show two similar bands, though with the longer-wave one weakened, as in methyl phenyl sulphide (Fig. 1), or reduced to a shoulder, as in *cyclo*hexyl phenyl sulphide (Koch, *loc. cit.*).

FIG. 1.*



* In the formulæ used in the Figures all rings are aromatic.

We infer that the bands represent distinct transitions of π electron states, and that neither necessitates any radical extension of conjugation to cover both phenyl rings. From its intensity and position, the shorter-wave band is identified as a perturbed form of the $\mathbf{B}_{2u}$ transition of the π^6 chromophore of benzene. The longer-wave band is ascribed to a similarly perturbed form of the transition of the 8-electron chromophore labelled $\pi^*_{(8)}$, ideally consisting of one unshared pair of sulphur electrons conjugated with the benzene π-shell. The assumption that the sulphur is conjugated essentially with one ring at a time (though, of course, with interchange) is the consistent basis on which we have attempted to interpret the spectra of substitution products, as is indicated below. This is reasonable in view of the non-planarity of diphenyl sulphide, which is expected greatly to reduce the significance of conjugative interaction between the benzene rings by way of sulphur :

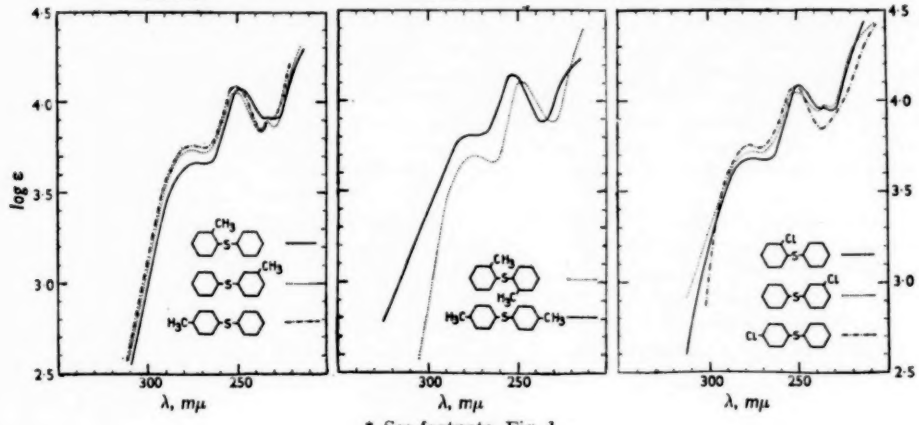
(The asterisks locate the chromophores, *i.e.*, the groups of electrons which together accept most of the disturbance of excitation.)

(2) *Methyl and Halogeno-derivatives of Diphenyl Sulphide* (Table 1, Nos. 2—9, Figs. 2—4).—Just as nuclear methyl substituents produce no considerable change in the absorption spectra of thiophenol and methyl phenyl sulphide so neither methyl nor chlorine substituents bring about any radical change of spectrum in diphenyl sulphide. It is inferred that the interaction of these substituents with either the π^6 or the $\pi^*_{(8)}$ chromophore is small enough to be considered a perturbation, which does not change the essential character of either upper electronic state.

(3) *Amino-derivatives of Diphenyl Sulphide* (Table 1, Nos. 10—17, Figs. 5—7).—In contrast to the above, the spectral effect of an amino-substituent is very marked, as is illustrated by the *p*-amino-derivative (Fig. 6); the two original bands of diphenyl sulphide become enveloped by the contour of a single stronger band, having its maximum at 256 mμ. A *p'*-methyl substituent makes no difference to this result, and even a *p'*-amino-group only displaces the single band slightly towards longer wave-lengths, making it a little stronger. But with any of these amino- or diamino-compounds in hydrochloric acid, the single strong band breaks into two and weakens to give a spectrum almost identical with that of diphenyl sulphide. If the amino-groups are acetylated, one observes an

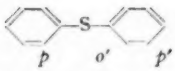
incipient splitting of the single strong band; but still the spectrum retains the general character of those of aminodiphenyl sulphides, rather than that of non-aminated diphenyl sulphide. Exceptions arise when the acetamido-groups are *ortho*-situated with respect to the sulphide bond; the spectrum then becomes practically identical with that of free diphenyl sulphide.

FIG. 2.* FIG. 3.* FIG. 4.*



* See footnote, Fig. 1.

TABLE 1.

Substituents in 						Characteristic points: up to 240 mμ		240—260 mμ		260—280 mμ		M. p. (uncorr.)		
No.	*o*	*m*	*p*	*o'*	*p'*	λ	log ε	λ	log ε	λ	log ε	Fig.	or b. p.	Ref.
1	—	—	—	—	—	—	—	250	4·08	274	3·75	1	294°/ 760 mm.	(a)
2	CH_3	—	—	—	—	(232)	3·93	248	4·08	272	3·67	2	306·5°/ 760 mm.	(b)
3	—	CH_3	—	—	—	232	3·90	250	4·06	275	3·74	2	309·5°/ 760 mm.	(c)
4	—	—	CH_3	—	—	230 *	3·92	250	4·09	274	3·76	2	15·7°	(c)
5	CH_3	—	—	CH_3	—	—	—	248	4·11	274	3·70	3	64°	(d)
6	—	—	CH_3	—	CH_3	—	—	252	4·16	276	3·83	3	56—57°	(d)
7	Cl	—	—	—	—	(234)	3·96	249	4·09	275	3·69	4	186°/40 mm.	(e)
8	—	Cl	—	—	—	(234)	3·98	250	4·05	273	3·73	4	186°/30 mm.	(e)
9	—	—	Cl	—	—	—	—	250·5	4·08	275	3·76	4	188°/35 mm.	(f)
10	NHAc	—	—	—	—	—	—	246	4·25	(276)	3·76	5	86°	(g)
11	NHAc	—	—	—	CH_3	—	—	248	4·27	275 *	3·82	5	108°	(h)
12	—	—	NH_2	—	—	—	—	256	4·28	—	—	6	93°	(i)
13	—	—	NHAc	—	—	—	—	258	4·30	280 *	4·17	6	146°	(i)
14	—	—	NH_2	—	CH_3	—	—	258	4·31	—	—	7	74°	(j)
15	—	—	NHAc	—	CH_3	—	—	259	4·32	280 *	4·14	7	108—109°	(k)
16	—	—	NH_2	—	NH_2	—	—	—	—	264	4·39	—	108°	(i)
17	—	—	NHAc	—	NHAc	—	—	250 *	4·32	271	4·43	—	223—224°	(l)

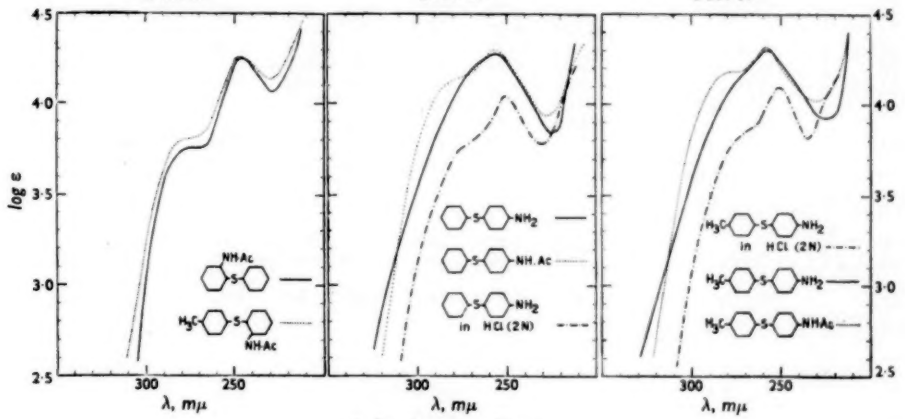
(a) Supplied by Fraenkel and Landau, Berlin; (b) Weedon and Doughty, *Amer. Chem. J.*, 1905, **33**, 417; (c) Bourgeois, *Ber.*, 1895, **28**, 2323; (d) Purgotti, *Gazzetta*, 1890, **20**, 30; (e) Passerini, *Boll. sci. Fac. Chim. Ind.* (*Bologna*), 1950, **8**, 122; (f) Michaelis and Godchaux, *Ber.*, 1891, **24**, 763; (g) Mauthner, *ibid.*, 1906, **39**, 3598; (h) By acetylation, with acetic anhydride in acetic acid solution, of the amino-derivative prepared as indicated by Gilman, Smith, and Broadbent, *J. Amer. Chem. Soc.*, 1947, **69**, 2053; (i) Kehrman and Bauer, *Ber.*, 1896, **29**, 2363; (j) Law and Johnson, *J. Amer. Chem. Soc.*, 1930, **52**, 3623; (k) Meyer and Heiduschka, *J. pr. Chem.*, 1903, **68**, 267; (l) Nietzki and Bothof, *Ber.*, 1894, **27**, 3261.

The inference drawn from these observations is that the band at about 256 mμ represents the unresolved envelope of bands of several upper electronic states, among them those already considered, and also an upper state of the $\pi^*_{(N)}$ chromophore, $\cdot C_6H_4\cdot\ddot{N}H_2$, the internal coupling in which, like that in $C_6H_5\cdot S\cdot$, is strong enough to require its distinctive

recognition, and is too strong to admit of convenient classification of its upper state as a perturbed form of the absorption-forbidden benzene state. In acid, the last-mentioned chromophore has no effect for obvious reasons. Acetylation reduces its role for equally well understood causes. And, in its dependence on an *o*-acetamido-group, it again has no role, because of the steric inhibition of acetamido-to-aryl conjugation.

(4) *Nitrodiphenyl Sulphides* (Table 2, Nos. 18, 32, 35; Fig. 8).—It is convenient to compare the spectra of the three methyl nitrophenyl sulphides with those of the nitrodiphenyl sulphides: methyl *o*- and *p*-nitrophenyl sulphide have been examined by Fehnel and Carmack (*J. Amer. Chem. Soc.*, 1949, **71**, 2889), and *o*- and *p*-nitrodiphenyl sulphides by Koch (*loc. cit.*), with results which agree with ours: the latter are included in the more complete series of Fig. 8. This shows that the salient features of the spectra of the methyl nitrophenyl sulphides recur slightly modified in the spectra of the corresponding nitrodiphenyl sulphides. A strong suggestion is thereby conveyed that the same chromophores are in action in both cases, independently of the presence of a second aromatic ring in the nitrodiphenyl sulphides.

FIG. 5.* FIG. 6.* FIG. 7.*



* See footnote, Fig. 1.

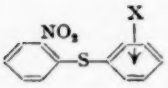
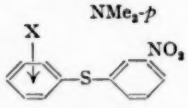
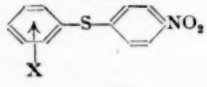
As to absorption on the long-wave side of 300 mμ, doubtless the responsible system involves the nitro-group. For both sets of nitro-compounds the intensities of the band in this region are in the order *p*->*o*->*m*-. This is the expected order of ability of the NO_2 and SR groups to conjugate through the intervening ring: for *ortho*-conjugation is restricted by non-planarity, and *meta*-conjugation is not possible. The wave-lengths of these long-wave bands are in the order *o*-> *m*- > *p*-. The longer wave-length of the *o*- than of the *p*-bands can be understood, just as for quinones, or nitroanilines, or nitrophenols, because the longest path through the conjugated system is longer in *ortho*- than in *para*-conjugated systems. As a summary of these conclusions, the long-wave chromophores may be indicated as follows:

$$\underbrace{o\text{-}NO_2\cdot C_6H_4\cdot SR}_{*\ (\pi^{10})} \qquad \underbrace{m\text{-}NO_2\cdot C_6H_4\cdot SR}_{*\ (\pi^{8})} \qquad \underbrace{p\text{-}NO_2\cdot C_6H_4\cdot SR}_{*\ (\pi^{10})}$$

As to the shorter-wave side of 300 mμ, one has first to notice that the absorption of *o*-nitrodiphenyl sulphide is the same as that of diphenyl sulphide, just as that of methyl *o*-nitrophenyl sulphide is like that of methyl phenyl sulphide. Presumably the *o*-nitro-group, twisted, as it must be, from the ring-plane, does not impair the participation of the ring in the chromophores of the non-nitrated parents. The *m*-nitro-compounds show strongly diminished absorption in the 274-mμ region, but not in the 250-mμ region. This

seems consistent since the *m*-nitro-groups will be functionally conjugated with their own rings, but not through those rings with sulphur; yet the conjugation between the nitro-groups and their benzene rings will interfere with the conjugation of the latter with sulphur, on which the $\pi^{s}_{(B)}$ chromophore depends. The *para*-compounds show further weakening

TABLE 2.

X in No.		Characteristic points: 210—250 mμ λ	log ε	260—300 mμ λ	log ε	beyond 300 mμ λ	log ε	Fig.	m. p. (uncorr.)	Ref.
										
18	—	240	4·24	(268)	3·86	368	3·65	8	79°	(a)
19	CH_3-*o*	240	4·23	270	3·89	370	3·68	—	87—88	(b)
20	CH_3-*m*	241	4·23	270 *	3·86	369	3·63	—	86	(b)
21	CH_3-*p*	242	4·25	270	3·89	371	3·67	—	89—90	(b)
22	Cl-*o*	240	4·25	275	3·87	364·5	3·65	9	121—122	(c)
23	Cl-*m*	238	4·25	275	3·85	365	3·64	9	107—108	(c)
24	Cl-*p*	225	4·35	275	3·83	367	3·71	9	94	(c)
		(240)	4·27	—	—	—	—			
25	Br-*m*	238	4·28	273	3·83	363	3·64	9	107—108	(c)
26	Br-*p*	232	4·38	275·5	3·89	364	3·66	9	108—109	(c)
		(236)	4·37	—	—	—	—			
27	I-*m*	238	4·40	270	3·87	364	3·66	9	99—100	(c)
28	I-*p*	240	4·44	275	3·94	365·5	3·67	9	130—131	(c)
29	NH_2-*p*	242	4·36	265	4·29	373	3·67	10	102	(d)
30	NHAc-*p*	235	4·40	272	4·22	371	3·71	10	195	(e)
		245	4·44	—	—	—	—			
31	NMe_2-*p*	240	4·28	282	4·41	375	3·67	10	187—188	(f)
X in 										
32	—	250	4·28	—	—	336—346	3·02	8	42·5	(g)
33	CH_3-*p*	250	4·31	—	—	340—344	2·98		60·5—61	(c)
		—	—	—	—	346	3·02			
34	NMe_2-*p*	250	4·28	280	4·48	362	2·95	10	119—120	(c)
X in 										
35	—	—	—	260 *	3·70	337	4·13	8	55	(h)
36	CH_3-*o*	—	—	262 *	3·62	338	4·15	—	64	(b)
37	CH_3-*m*	—	—	262 *	3·69	338	4·12	—	47	(b)
38	CH_3-*p*	222	4·23	262 *	3·70	339	4·13	—	81·5	(i)
39	Cl-*o*	—	—	260 *	3·82	332	4·09	9	115	(b)
40	Cl-*m*	—	—	260 *	3·80	333	4·12	9	72	(b)
41	Cl-*p*	225	4·27	(262)	3·76	336	4·12	9	84—85	(b)
42	Br-*m*	—	—	260 *	3·77	330	4·11	9	71—72	(c)
43	Br-*p*	229·5	4·27	265	3·81	334	4·11	9	94	(j)
44	I-*m*	231	4·28	260 *	3·78	332	4·11	9	81—82	(c)
45	I-*p*	240	4·26	270	3·88	336	4·11	9	101—102	(j)
46	NH_2-*p*	245	4·12	265	4·21	345	4·12	10	144	(k)
47	NHAc-*p*	248	4·29	270	4·15	339	4·14	10	193	(k)
48	NMe_2-*p*	—	—	279	4·37	342	4·12	10	181	(l)

(a) Roberts and Turner, *J.*, 1926, 1208; (b) Gilman, Smith, and Broadbent, *J. Amer. Chem. Soc.*, 1947, **69**, 2055; (c) Passerini, *Boll. sci. Fac. Chim. Ind.* (*Bologna*), 1950, **8**, 122; (d) Hodgson, Wolf, and Rosenberg, *J.*, 1930, 181; (e) By acetylation, with acetic anhydride in acetic acid solution, of the amino-derivative; (f) Zincke and Farr, *Annalen*, 1912, **391**, 93; (g) Hammick and Williams, *J.*, 1938, 211; cf. Passerini (c); (h) Hodgson, Reggie, and Smith, *J.*, 1937, **1636**; (i) Law and Johnson, *J. Amer. Chem. Soc.*, 1930, **52**, 1930, **52**, 3623; (j) Amstutz, Fehnel, and Woods, *ibid.*, 1947, **69**, 1923; (h) Raiziss, Clemence, Severac, and Moltzsch, *ibid.*, 1939, **61**, 2763; (l) Zincke and Lenhardt *Annalen*, 1924, **400**, 24.

of absorption in the 274-mμ region, and also weakening towards 250 mμ. This agrees with the idea that the nitro-group is now through-conjugated, so that it can seriously disturb the whole spectral behaviour of the molecule. Only *p*-nitrodiphenyl sulphide shows a vestigious band near 260 mμ, arising, one may presume, from excitation of the π^{6} chromophore of the benzene ring remote from the nitro-group.

(5) ***Nitrophenyl Tolyl Sulphides and Halogenophenyl Nitrophenyl Sulphides*** (Table 2, Nos. 21—28, 33, 36—45; Fig. 9).—The spectra of the nitrodiphenyl sulphides are modified only to a trifling extent by methyl substitution in the non-nitrated ring, and only in detail

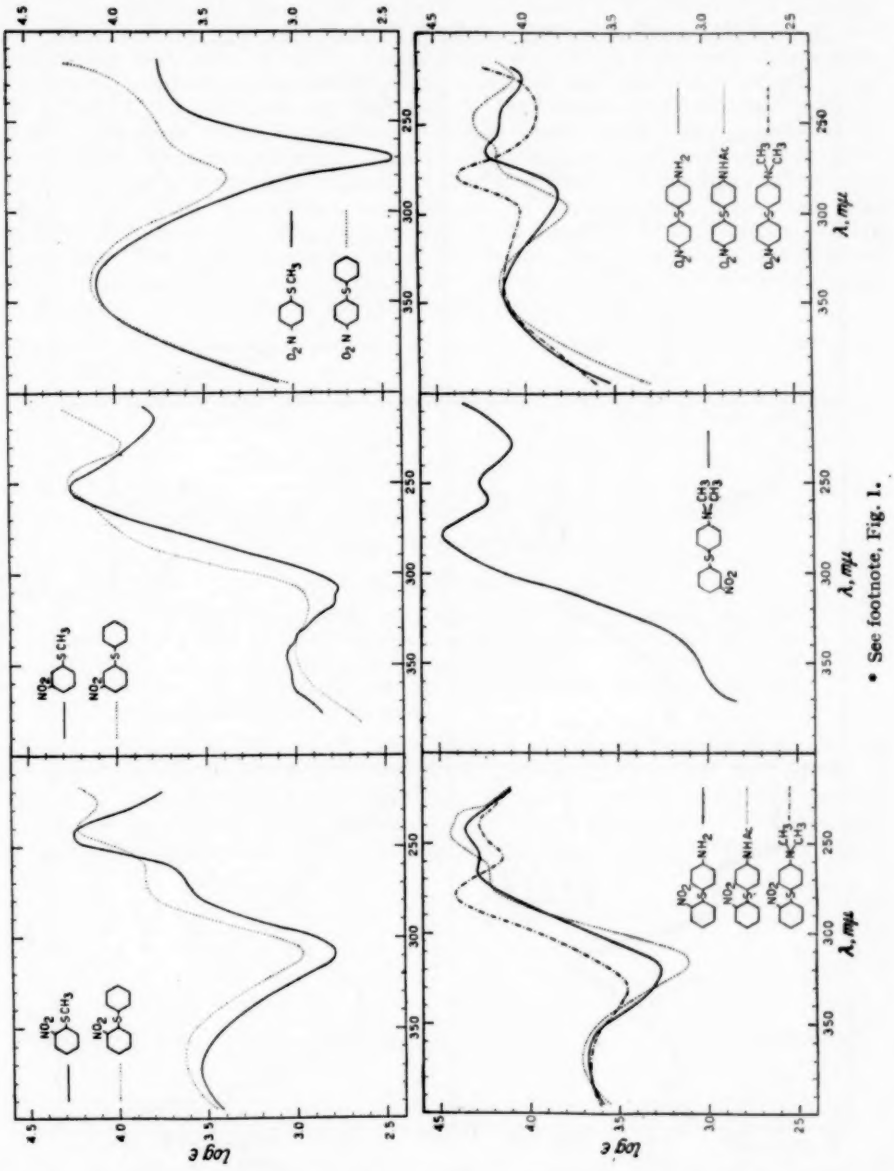


FIG. 8.*

* See footnote, Fig. 1.

by halogeno-substitution in that ring (Fig. 9). Accordingly, the broad features of all these spectra are covered by the discussion of the preceding section.

As to the detailed differences, one of the more general is that halogeno-substitution shifts the bands credited to the nitro-containing π^{10} chromophore slightly (1—7 mμ) towards

shorter wave-lengths. This could be an electrostatic effect arising from the electronegativity of the halogen.

(6) *Amino-derivatives of Nitrodiphenyl Sulphides* (Table 2, Nos. 29—31, 34, 46—48; Fig. 8).—It is a striking feature of these spectra that, while the parts on the shorter-wave

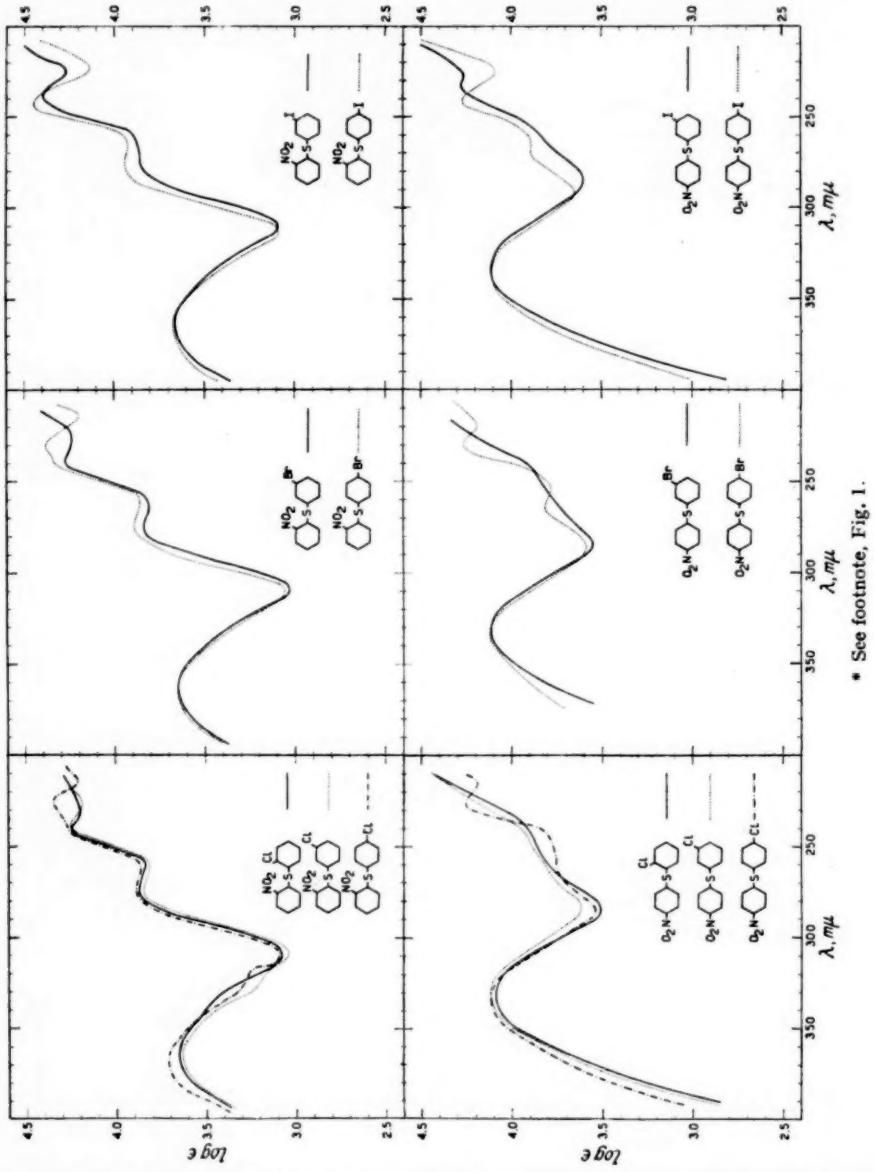


FIG. 9.* * See footnote, Fig. 1.

side of 300 mμ vary considerably from compound to compound, the longer-wave bands, ascribed to the π^{10} chromophore of *o*- and *p*-$NO_2{\cdot}C_6H_4{\cdot}S{\cdot}$, are practically unaltered by the various NX_2 substituents. From this we conclude that there is no functional through-conjugation between the NX_2 and the NO_2 groups, a result which should be expected in

consequence of the non-coplanarity of the benzene rings. The band attributed to the chromophore π^8 of the group m-$NO_2{\cdot}C_6H_4{\cdot}$ is partly overlapped, but not necessarily otherwise altered in the dimethylamino-derivative (No. 34).

As to the region beyond 300 mμ, the intense bands of the dimethylamino-compounds at 280 mμ are ascribed to the $\pi^8_{(18)}$ chromophore $\cdot C_6H_4{\cdot}NMe_2$ of dimethylaniline (Remington, *J. Amer. Chem. Soc.*, 1945, **67**, 1838; Klevens and Platt, *ibid.*, 1949, **71**, 1714; Robertson and Matsen, *ibid.*, 1950, **72**, 1543). The bands at 265—272 mμ in the amino-compounds, and their acetyl derivatives, are similarly assigned (Doub and Vanderbelt, *loc. cit.*). The bands at 240—250 mμ in the *o*- and *m*-dimethylamino-compounds are assigned to the π^6 benzene chromophore, which is weakened to ineffectiveness in the *p*-nitro-compound, by nitro-to-sulphide through-conjugation; just as the same chromophore, though it is active in methyl *o*- and *m*-nitrophenyl sulphide, is greatly weakened in methyl *p*-nitrophenyl sulphide (cf. Fig. 8). The bands near 240 mμ of the nitroamino-compounds and their acetyl derivatives are tentatively attributed to the same π^6 chromophore of the nitrated ring. The apparent duplication of this band on acetylation of the *p*-amino-*o*-nitro-compound may be connected with the circumstances that acetanilide itself (Klingstedt, *Z. physikal. Chem.*, 1928, *B*, **1**, 74) has a band in this region.

This work has benefitted by an exchange of views with Professor C. K. Ingold, F.R.S., and Dr. D. P. Craig.

ISTITUTO DI CHIMICA INDUSTRIALE DELL' UNIVERSITÀ,
BOLOGNA.

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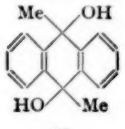
207. *Substituted Anthracene Derivatives. Part VI.** 9-n-*Prop*-1′-*enyl*-10-n-*propylanthracene.*

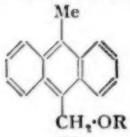
By G. M. BADGER.

9-*n*-Prop-1′-enyl-10-*n*-propylanthracene has been obtained by the addition of a little hydrochloric acid to a boiling alcoholic solution of 9 : 10-dihydro-9 : 10-dihydroxy-9 : 10-di-*n*-propylanthracene. The structure of the product has been confirmed by an independent synthesis, and the mechanism of the reaction is discussed.

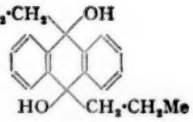
In Part III (Badger and Pearce, *J.*, 1950, 2314) it was shown that the acid-catalysed dehydration of 9 : 10-dihydro-9 : 10-dihydroxy-9 : 10-dimethylanthracene (I) leads to the formation of 9-alkoxymethyl-10-methylanthracene (II) the nature of the alkoxy-group depending on the alcohol used as solvent. A mechanism involving a 1 : 5-anionotropic shift of the initial product of dehydration was suggested to account for this observation.



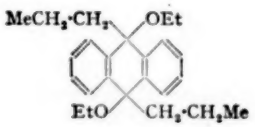
(I)



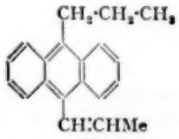
(II)



(III)



(IV)



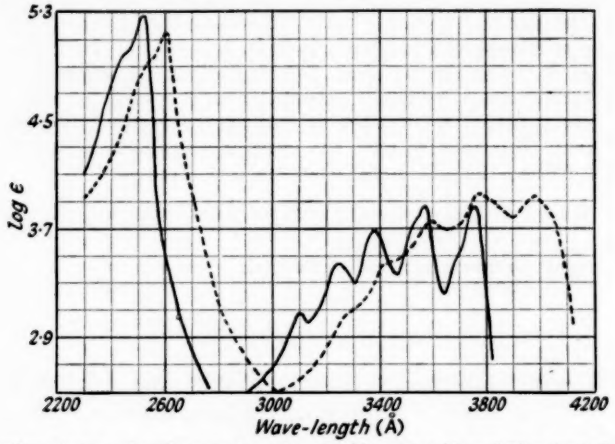
(V)

In order to examine the reaction further, however, it seemed desirable to study the acid-catalysed dehydration of some other diols, particularly those having alkyl groups other than methyl.

* Part V, *J.*, 1952, 1112.

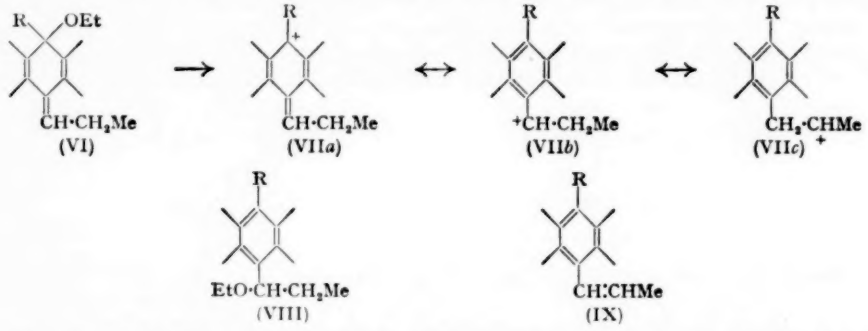
It has now been found that when a boiling alcoholic solution of either 9 : 10-dihydro-9 : 10-dihydroxy-9 : 10-di-*n*-propylanthracene (III) or its diethyl ether (IV) is treated with a little hydrochloric acid, both oxygen atoms are lost and 9-*n*-prop-1′-enyl-10-*n*-propylanthracene (V) results.

The diethyl ether (IV) was prepared from the diol (III) by use of cold ethanol and a little mineral acid, and it seems likely that the initial effect of adding acid to a boiling alcoholic solution of the diol is also to form the ether. Removal of one molecule of ethanol would then give the intermediate (VI), and the transformation of this into the final product (IX) might be expected to proceed in two ways. For example, the elimination of a second



Ultra-violet absorption spectra of anthracene (——) *and of* 9-n-*prop*-1′-*enyl*-10-n-*propylanthracene* (– – –), *in ethanol. The latter has maxima (and log* ε*) at* 2605 (5·13), 3595 (3·76), 3775 (3·96), *and* 3930 Å, 3·93); *and points of inflexion at* 3250 (3·02), *and* 3400 Å (3·42).

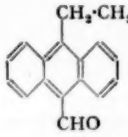
ethoxy-group from (VI) would give the mesomeric ion (VII), and removal of a proton from (VII*b*) would give (IX) directly. Alternatively, the intermediate (VI) would be expected to undergo 1 : 5-anionotropic rearrangement (*via* VII) to give the ether (VIII). This compound could not be isolated from the reaction mixture even after runs carried out under



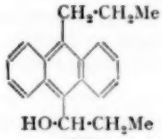
somewhat milder conditions than usual. Nevertheless, it may be an intermediate, for further heating with acid would be expected to remove the ethoxy-group and again give the ion (VII*b*). In either case, the driving force of the reaction is clearly the tendency towards increased conjugation and increased resonance stabilisation.

This mechanism is also supported by the nature of the independent synthesis of the product. 9-*n*-Propylanthracene was prepared by Sieglitz and Marx's method (*Ber.*, 1923, **56**, 1619) and was converted into 10-*n*-propyl-9-anthraldehyde (X) by Fieser's formanilide

aldehyde synthesis (*Org. Synth.*, 1940, **20**, 11). After treatment of (X) with ethylmagnesium bromide, the crude alcohol (XI) was obtained. This could not be obtained pure, and was accordingly treated with boiling ethanol containing a little hydrochloric acid. The 9-*n*-prop-1′-enyl-10-*n*-propylanthracene (V) obtained in this way was shown to be identical with that obtained by the first method.



(X)



(XI)

The structure of the product is also supported by its ultra-violet absorption spectrum (see figure) which is of the anthracene type. The very large bathochromic shift, however, is noteworthy; such a large shift would be expected from an anthracene derivative having a substituent (such as a propenyl group) capable of strong conjugation with the ring system.

Experimental

9 : 10-*Dihydro*-9 : 10-*dihydroxy*-9 : 10-*di*-n-*propylanthracene*.—The following method proved more convenient than that given in the literature. A mixture of anthraquinone (10 g.), magnesium (5 g.), anhydrous ether (60 c.c.), and anhydrous, thiophen-free benzene (60 c.c.) was treated with excess of *n*-propyl bromide (20 c.c.). After the reaction had abated somewhat, the mixture was refluxed for an hour, then cooled and decomposed with ice and ammonium chloride. The product was isolated in the usual way and freed from unchanged anthraquinone with alkaline dithionite. The yield of diol was 3·9 g.

9 : 10-*Diethoxy*-9 : 10-*dihydro*-9 : 10-*di*-n-*propylanthracene*.—A solution of the above diol (0·25 g.) in absolute ethanol, was treated (below 15°) with 2 drops of concentrated sulphuric acid in a little ethanol. After 1 hour the crystals (0·25 g.) were collected and recrystallised from ethanol. 9 : 10-*Diethoxy*-9 : 10-*dihydro*-9 : 10-*di*-n-*propylanthracene* formed prisms, m. p. 211—213° (Found: C, 82·0; H, 9·1. $C_{24}H_{32}O_2$ requires C, 81·8; H, 9·1%).

10-n-*Propyl*-9-*anthraldehyde* (X).—A mixture of 9-*n*-propylanthracene (10 g.), methylformanilide (10 c.c.), phosphorus oxychloride (10 c.c.), and chlorobenzene (10 c.c.) was heated on the water-bath for 1½ hours. After the red solution had cooled, sodium acetate (30 g.) in water (100 c.c.) was added. The solvents were removed by rapid steam-distillation, and the product (8·6 g.) was recrystallised from alcohol (charcoal). 10-n-*Propyl*-9-*anthraldehyde* formed golden plates, m. p. 102—104° (Found: C, 87·2; H, 6·4. $C_{18}H_{16}O$ requires C, 87·1; H, 6·5%).

9-n-*Prop*-1′-*enyl*-10-n-*propylanthracene* (V).—(i) A solution of the diol (5·0 g.) in boiling absolute ethanol (150 c.c.) was treated with dilute hydrochloric acid (10 c.c.). A white precipitate formed almost at once and this gradually dissolved on further heating. After two hours, water was added, and the mixture set aside overnight. The gummy precipitate was then dissolved in benzene, the benzene solution washed and dried, and the solution evaporated on the steam-bath. After being set aside overnight in the refrigerator, the product was mostly crystallised; it was purified by recrystallisation from alcohol and sublimation at 140°/0·5 mm. 9-n-*Prop*-1′-*enyl*-10-n-*propylanthracene* (1·6 g.) formed yellow blades (from alcohol), m. p. 125—126° (Found: C, 92·3; H, 7·7. $C_{20}H_{20}$ requires C, 92·2; H, 7·8%).

Similar results were obtained by using the diethyl ether instead of the diol.

The *s*-trinitrobenzene *complex* was prepared in alcohol and recrystallised from the same solvent; it formed shining red needles, m. p. 131° after slight sintering (Found: C, 66·25; H, 5·0. $C_{20}H_{20},C_6H_3O_6N_3$ requires C, 65·95; H, 4·9%). The hydrocarbon could not be recovered from the complex by chromatography on alumina; but the following method proved satisfactory. The complex was dissolved in boiling alcohol, and a warm solution of stannous chloride in concentrated hydrochloric acid was gradually added until the red colour was completely discharged. Water was then added to the cooled mixture, and the hydrocarbon was collected, washed, and recrystallised.

(ii) 10-*n*-Propyl-9-anthraldehyde (8·3 g.) was gradually added, at room temperature, to a Grignard solution prepared from ethyl bromide (15 c.c.), magnesium (2·5 g.), anhydrous ether (70 c.c.), and anhydrous, thiophen-free benzene (70 c.c.). After 3 hours the mixture was warmed

for ½ hour on the steam-bath. The cooled reaction mixture was then decomposed with ice and ammonium chloride. The organic layer was washed with water, dried, and evaporated, but the resulting gum could not be induced to crystallise. The crude product was therefore dissolved in boiling ethanol, and dilute hydrochloric acid (10 c.c.) added. After being boiled for 2 hours and then cooled, water was added, and the product extracted with benzene. Evaporation of the solvent gave crystalline 9-*n*-prop-1′-enyl-10-*n*-propylanthracene (3·6 g.). After crystallisation from alcohol, it formed yellow blades, m. p. 125—126° not depressed by admixture with a specimen prepared as above. Furthermore, it gave a red *s*-trinitrobenzene complex, m. p. 131° either alone or mixed with a specimen of the complex prepared from the hydrocarbon above.

My thanks are due to Mr. R. S. Pearce for the absorption spectra. Microanalyses were carried out by the C.S.I.R.O. Microanalytical Laboratory, Melbourne.

UNIVERSITY OF ADELAIDE. [*Received, November 10th*, 1951.]

NOTES.

208. *Anionic Polymerisation. Part III.* The Polymerisation of Styrene in Liquid Ammonia Catalysed by Potassium.*

By N. S. WOODING and W. C. E. HIGGINSON.

RECENT copolymerisation studies (Landler, *Compt. rend.*, 1950, **230**, 539; Mayo and Walling, *Chem. Reviews*, 1950, **46**, 191; Walling, Briggs, Cummings, and Mayo, *J. Amer. Chem. Soc.*, 1950, **72**, 48) have indicated that the mechanism of polymerisation by alkali metals, both in liquid ammonia and in the absence of solvent, differs from that obtaining with acid (Friedel–Crafts) catalysts or with free-radical initiators. It seems probable that the polymerisation reaction takes place by an anionic chain mechanism, and comparison of the results obtained in the alkali metal–liquid ammonia system with those using known anionic catalysts supports this view (Beaman, *ibid.*, 1948, **70**, 3115).

The polymerisation of styrene in liquid ammonia by the amide ion, NH_2^-, has been studied by us (*J.*, 1952, 760) and the dependence of the rate of monomer disappearance and of the molecular weight upon reactant concentrations and upon temperatures has been established. A few experiments have also been done with potassium as catalyst in place of potassium amide. Styrene was again used as monomer. The results of rate experiments at −33·5° are shown below.

$[C_8H_8]$, mole/l.	[K], mole/l.	Rate $= d(1/[C_8H_8])/dt$, l. mole^{-1}, min.$^{-1}$	k, l.$^{1\frac{1}{2}}$ mole$^{-1\frac{1}{2}}$ min.$^{-1}$
0·197	0·0075	0·153	1·77
0·190	0·0340	0·318	1·72

As in the previous work, good second-order plots were obtained for the rate of disappearance of monomer (M), and the rate was proportional to the square root of the initial potassium concentration, as shown by the two similar values of the overall reaction velocity constant k, calculated from the expression $-d[M]/dt = k[M]^2[K]^{\frac{1}{2}}$. The average value for k, 1·75, compares with the average value, 2·81, obtained for k' ($-d[M]/dt = k'[M]^2[KNH_2]^{\frac{1}{2}}$) for the potassium amide-catalysed polymerisation at the same temperature, −33·5° (see Higginson and Wooding, *loc. cit.*).

The molecular weight of polymer formed in experiments with initial monomer concentration 0·190 mole/l., the reaction being stopped after 32% of the styrene had reacted, was 4450 (intrinsic viscosity, $[\eta] = 0·160$). The polymer was found to contain nitrogen, and one nitrogen atom being assumed per polymer molecule, as in the amide-ion catalysed polymerisation of styrene, the number-average molecular weight obtained from the nitrogen

* Part II, *J.*, 1951, 774.

content was 3080 and 2980 in two determinations. The discrepancy between the molecular weight values obtained by these two methods is little greater than was found previously in some instances in the experiments using potassium amide. The viscosity molecular weight of polystyrene produced from a reaction mixture of the same initial styrene concentration with potassium amide as catalyst is *ca.* 3500 at 32% reaction (approximately 60% higher than the value obtained at 100% reaction).

There is thus considerable similarity between the experimental findings for the potassium amide- and the potassium-catalysed polymerisation of styrene in liquid ammonia. In both cases there is a second-order dependence of the rate of disappearance of styrene on the styrene concentration. The rate of disappearance of styrene is proportional to $[KNH_2]^2$ in the first case, and to $[K]^2$ in the second. The overall rate constants k' and k are numerically similar in the two cases. The viscosity molecular weight of polystyrene prepared with potassium as catalyst is similar to that expected from the potassium amide-catalysed polymerisation under otherwise identical conditions. This overall similarity makes it probable that the mechanism of the potassium-catalysed polymerisation is the same as that established for the potassium amide-catalysed reaction, *i.e.*, as shown by the three equations (with R = Ph) in Part I (*J.*, 1952, 760).

In the potassium-catalysed polymerisation, we suggest that the amide (NH_2^-) ion, which is the true catalyst, is formed in the reduction of styrene by potassium :

$$(O)\ 2K + CH_2{:}CHPh + 2NH_3 \longrightarrow 2K^+ + CH_3{\cdot}CH_2Ph + 2NH_2^-$$

Wooster and Ryan (*J. Amer. Chem. Soc.*, 1934, **56**, 1133) have prepared ethylbenzene in 50% yield by mixing approximately equivalent quantities of sodium and styrene in liquid ammonia solution.

Reaction (*O*) must be rapid to account for the similarity between the rates of the potassium- and the potassium amide-catalysed polymerisations. This is borne out by (*a*) the almost instantaneous disappearance of the blue colour of potassium in liquid ammonia on admixture with the styrene solution, though the half-life of the polymerisation reaction is of the order 15—30 minutes, and (*b*) the absence of any red colour in the solution characteristic of carbanions of the type $Ph-\overset{(-)}{C}<$ which might be formed as intermediates in significant concentration. It is possible that such carbanion intermediates, if formed, would act as initiating species in addition to the amide ion. However, as the nitrogen content of the polymer is close to that expected for amide-ion initiation alone (carbanion initiation would not introduce nitrogen into the polymer), it seems probable that such side reactions are relatively insignificant, if they occur at all. The detailed steps by which reaction (*O*) takes place are at present unknown, but this is unimportant if, as appears probable, the overall reaction occurs rapidly and reactions of intermediates with styrene can be neglected.

The reaction scheme suggested above, *i.e.*, the rapid reduction of monomer by potassium leading to the formation of amide ions which can initiate an anionic polymerisation, is also likely to hold with other vinyl monomers. In certain cases the potassium may reduce groups other than the ethylenic double bond, but as such reduction will usually result in the formation of amide ions, *e.g.*, $2K + 2NH_3 + X \longrightarrow 2K^+ + 2NH_2^- + XH_2$, similarities are in general to be expected between the potassium amide- and potassium-catalysed polymerisations of other monomers in liquid ammonia as solvent. If XH_2 is comparatively acid, so that by reaction with the amide ion the reduction leads to the formation of anions which are weaker bases, and which in many cases (cf. Wooding and Higginson, *J.*, 1952, 774) are ineffective as anionic initiators, alkali metal-catalysed polymerisation is unlikely to occur, provided that the amide ions have been completely removed.

Experimental.—Experiments were carried out in absence of air at −33·5° in the apparatus described by Higginson and Wooding (*loc. cit.*). The rate of monomer disappearance was determined by the sampling method used in the potassium amide-catalysed polymerisation studies. Polymer was purified as before by precipitation from ethyl methyl ketone solution with methanol and was dried in a vacuum (P_2O_5). The viscosity of a polymer solution in benzene was determined at 25° in an Ostwald viscometer, and the molecular weight calculated

from the intrinsic viscosity by Kemp and Peters's equation (*Ind. Eng. Chem.*, 1942, **34**, 1097). Though the use of this particular molecular weight–intrinsic viscosity relation may be questioned, comparison of molecular weights found by using this relation in each case is essentially a comparison of intrinsic viscosities, and so the similarity between molecular weights found in otherwise identical conditions in the potassium amide- and potassium-catalysed polymerisations is legitimately established. Nitrogen determinations were made by using the Kjeldahl method as before.

Our thanks are offered to Messrs. Courtaulds Ltd. for a grant to one of us (N. S. W.).

THE CHEMISTRY DEPARTMENT,
THE UNIVERSITY, MANCHESTER. [*Received, September 25th*, 1951.]

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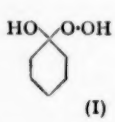
209. *The Structure of a Peroxide from* cyclo*Hexanone and Hydrogen Peroxide.*

By W. COOPER and W. H. T. DAVISON.

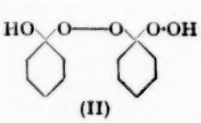
THE peroxide, m. p. 78—79°, obtained from equimolar amounts of *cyclo*hexanone and hydrogen peroxide was considered by Milas, Harris, and Panagiotakos (*J. Amer. Chem. Soc.*, 1939, **61**, 2430) to be 1-hydroxy*cyclo*hexyl hydroperoxide (I). Recently Criegee, Schnorrenberg, and Becke (*Annalen*, 1949, **565**, 7) have stated that it is actually 1-hydroperoxy*cyclo*hexyl 1-hydroxy*cyclo*hexyl peroxide (II) which can be regarded as a dehydration product of (I). They also consider that in solution (II) breaks down to give *cyclo*hexanone and 1 : 1-dihydroperoxy*cyclo*hexane.* Structure (I) was assumed by Cooper (*loc. cit.*) in a study of its thermal decomposition products, but it was pointed out that the results were not inconsistent with the view that other peroxides could also participate in the breakdown. It is, however, of considerable importance to decide between the alternative structures. The facts now reported support in general the structure and reactions proposed by Criegee *et al.* and give further information on the unusual properties of this compound.

The instability of the hydroperoxide caused difficulty in its purification and analyses of many samples were in agreement with structure (I); but repeated recrystallisation from light petroleum, followed by careful drying *in vacuo*, gave a compound analysis of which was correct for structure (II).

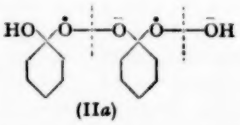
Reduction of the *solid* peroxide with aqueous ferrous sulphate gave mainly hexanoic and dodecane-1 : 12-dioic acid. These compounds would be formed from either structure, (II) forming a radical and an ion radical by one-electron addition to each of the peroxide links (cf. II*a*).



(I)



(II)



(II*a*)

On treatment with aqueous 2 : 4-dinitrophenylhydrazine hydrochloride complete decomposition occurred with the formation of one mole of the 2 : 4-dinitrophenylhydrazone per equivalent of the peroxide.

As the rival structures (I) and (II) have the same functional groups, direct elucidation of the structure from the infra-red spectrum would be difficult, other than by the use of molar extinction coefficients to determine the numbers of hydroxyl and hydroperoxyl groups. This was not attempted because of the additional complication of dissociation

* In the paper by Cooper (*J.*, 1951, 1340) the fact that these workers had described the dibenzoyl and di-*p*-nitrobenzoyl esters of this compound was overlooked.

in solution. The solid, in a mull with paraffin, showed not more than a trace of *cyclo*hexanone. In solution, however, dissociation occurred rapidly and the formation of *cyclo*hexanone was followed spectroscopically and shown to reach equilibrium after several hours (Table 1). The formation of *cyclo*hexanone in this way was observed in carbon

TABLE 1.

Time (hours)	0·25	0·50	0·75	1·75	2·75	3·75
$[C]/[P_0]$	0·12	0·30	0·37	0·57	0·62	0·60

$[P_0] = 0{\cdot}0390$ mole/l.

tetrachloride, styrene, *cyclo*hexane, and benzene. During this dissociation no change was apparent in the 3000—3800-cm.$^{-1}$ region, there being two hydroxyl absorptions only at 3370 and 3540 cm.$^{-1}$, the latter being stronger at greater dilutions (the 3370-cm.$^{-1}$ band is presumably that of hydrogen-bonded hydroxyl). Hydroxyl frequencies for hydroperoxides and alcohols are very similar (Shreve, Heether, Knight, and Swern, *Analyt. Chem.*, 1951, **23**, 282) but water has an absorption at 3450 cm.$^{-1}$ and the absence of this band is evidence against the bimolecular decomposition of (I) with the formation of (III), *cyclo*hexanone, and water.

The dissociation (at 30° in carbon tetrachloride) was increased by dilution (see Table 2) and this further supports structure (II). No displacement of the equilibrium was observed when the temperature was raised to 60°.

TABLE 2.

$[P_0]$	$[C_\infty]$	$[C_\infty]/[P_0]$	$[P_0]$	$[C_\infty]$	$[C_\infty]/[P_0]$	$[P_0]$	$[C_\infty]$	$[C_\infty]/[P_0]$
2·02	—	0	0·0336	0·0192	0·57 ± 0·02	0·00134	0·00135	1·01 ± 0·04
0·0840	0·0417	0·50 ± 0·02	0·0067	0·0053	0·79 ± 0·03	0·00027	0·000297	1·10 ± 0·04

$[P_0]$ is the initial concentration of peroxide. $[C_\infty]$ is the equilibrium concentration of *cyclo*hexanone (mole/l.).

That it was a reversible reaction was shown by the isolation of unchanged hydroperoxide by removal of the solvent at room temperature; there was no appreciable loss of peroxide-oxygen.

The new peroxide was apparently very stable in solution since at 70° it decomposed only very slowly in pure carbon tetrachloride or benzene; in impure solvents it decomposed autocatalytically with the formation of adipic acid.

The correct interpretation of these facts, and the formation of *cyclo*hexyl 1 : 1-diper-esters on treatment with acyl chlorides, would seem to be that suggested by Criegee *et al.* (*loc. cit.*):

$$HO{\cdot}O{\cdot}C_6H_{10}{\cdot}O{\cdot}O{\cdot}C_6H_{10}{\cdot}OH \rightleftharpoons C_6H_{10}O + C_6H_{10}(O{\cdot}OH)_2$$

This equilibrium would lead to the relation $[C_\infty]^2 = K([P_0] - [C_\infty])$, but its validity was not checked because the experimental results were insufficiently refined for accurate measurement of the small differences in the right-hand side of the equation.

Experimental.—1-*Hydroperoxy*cyclo*hexyl* 1-*hydroxy*cyclo*hexyl peroxide*. The peroxide was recrystallised from light petroleum (b. p. 60—80°) four times. The final slow recrystallisation from the solution of peroxide saturated at 30—40° gave long transparent needles which were dried in air and then in a vacuum at room temperature [Found: C, 58·4, 58·3; H, 9·2, 9·0; active O, 13·2 (iodometric determination with a solution of the peroxide in acetic acid and saturated aqueous potassium iodide). Calc. for $C_{12}H_{22}O_5$: C, 58·5; H, 9·0; active O, 13·0%].

Reduction of 1-*hydroperoxy*cyclo*hexyl* 1-*hydroxy*cyclo*hexyl peroxide with ferrous sulphate*. The peroxide (12 g.) was shaken with ferrous sulphate (60 g.) in water (500 ml.). The mixture became warm and dark brown ferric salts of the carboxylic acids separated. Shaking with acid gave an organic layer (8 g.) consisting of *cyclo*hexanone, hexanoic acid, and dodecane-1 : 12-dioic acid (m. p. 125°; diamide m. p. 186°).

Infra-red measurements were made with a Grubb Parsons single-beam spectrometer with a sodium chloride prism.

*cyclo*Hexanone in solution was determined from the intensity of the carbonyl stretching absorption at 1718 cm.$^{-1}$, at which frequency the other components did not interfere. To

check on the possible effect of hydrogen bonding from (II) and (III) a carbon tetrachloride solution, 0·04M. with respect to both *cyclo*hexanone and methyl alcohol, was examined. No anomalous absorption was observed, from which it was concluded that 1718 cm.$^{-1}$ was a satisfactory analytical frequency for the range of concentrations used. No attempt was made to increase the accuracy beyond about 2%.

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CHEMICAL RESEARCH DIVISION,
RESEARCH CENTRE, FORT DUNLOP. [*Received, October 6th*, 1951.]

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210. *Action of Acrylonitrile on Ethyl Aminomalonate and Ethyl Aminoacetate.*

By WESLEY COCKER, B. E. CROSS, and (MISS) JOAN MCCORMICK.

DURING another investigation, acrylonitrile was treated with ethyl aminomalonate. When potassium hydroxide was used as catalyst, the product isolated in fair yield (47%) was ethyl (2-cyanoethyl)aminomalonate (I). Its isomer (II) was not isolated from other unidentifiable products. That the product was substantially (I) follows from the fact that it gave a pure *p*-toluenesulphonyl derivative after one crystallisation, and on hydrolysis yielded glutamic acid which was substantially pure without crystallisation.

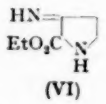
(I) $H_2N{\cdot}C(CO_2Et)_2{\cdot}CH_2{\cdot}CH_2{\cdot}CN$ $(EtO_2C)_2{\cdot}CH{\cdot}NH{\cdot}CH_2{\cdot}CH_2{\cdot}CN$ (II)

Glycine ester condensed with acrylonitrile in presence of potassium hydroxide or sodium ethoxide, the latter giving the larger yields of the product, ethyl N-2-cyanoethylaminoacetate (III; R = H). Its structure was determined by hydrolysis to β-(carboxymethylamino)propionic acid (IV) which was also obtained by the hydrolysis of its ester (V), prepared from ethyl aminoacetate and methyl β-chloropropionate. Although cyclisation

$EtO_2C{\cdot}CH_2{\cdot}NR{\cdot}CH_2{\cdot}CH_2{\cdot}CN$ (III)

$HO_2C{\cdot}CH_2{\cdot}NH{\cdot}CH_2{\cdot}CH_2{\cdot}CO_2H$ (IV)

$EtO_2C{\cdot}CH_2{\cdot}NH{\cdot}CH_2{\cdot}CH_2{\cdot}CO_2Me$ (V)



(VI)

(VII)

of (III; R = H) could yield either the substituted proline (VI), or 3-cyano-4-pyrrolidone (VII; R = H), the latter was expected since Cook and Reed (*J.*, 1945, 399) have shown that (III; R = Me) cyclises to give (VII; R = Me). That our product was (VII; R = H) is supported by the analytical results.

Experimental.—Ethyl (2-cyanoethyl)aminomalonate. A mixture of aminomalonic ester (2·8 c.c.), potassium hydroxide (0·7 g.), and benzene (5 c.c.) was slowly treated with acrylonitrile (1·14 c.c.). The yellow solution was stirred at room temperature for 4 hours and then refluxed for 1·25 hours. The *product* consisted of an oil (1·86 g.), b. p. 150—154°/18 mm. (Found: C, 52·6; H, 7·1. $C_{10}H_{16}O_4N_2$ requires C, 52·6; H, 7·0%). Its *p-toluenesulphonyl* derivative, once crystallised from alcohol, formed prisms, m. p. 153° unchanged by further crystallisation (Found: C, 54·0; H, 5·8. $C_{17}H_{22}O_6N_2S$ requires C, 53·4; H, 5·8%).

Hydrolysis. The above ester (I) (1·5 g.) was refluxed with 60% sulphuric acid (4 c.c.) for 4 hours. The product was isolated through its lead salt (cf. Cocker and Lapworth, *J.*, 1931, 1391), giving a solution, which on concentration deposited glutamic acid (0·11 g.), m. p. 192—194° (the literature gives figures varying from 190—200°). Its *p*-toluenesulphonyl derivative was obtained with m. p. 169—170° (undepressed by an authentic specimen) without purification.

Ethyl β-(cyanoethylamino)acetate (III; R = H) was obtained as an oil (2·94 g.), b. p. 150—152°/19 mm. (Found: C, 54·2; H, 8·2. $C_7H_{12}O_2N_2$ requires C, 53·8; H, 7·7%), from glycine ester (5 g.), acrylonitrile (3·2 c.c.), benzene (10 c.c.), and sodium ethoxide (sodium, 0·1 g., in

alcohol, 7 c.c.). Its p-*toluenesulphonyl* derivative crystallised from dilute alcohol as prisms, m. p. 71° (Found: C, 54·6; H, 5·7. $C_{14}H_{18}O_4N_2S$ requires C, 54·2; H, 5·8%).

β-(*Carboxymethylamino*)*propionic Acid*. The preceding compound (1·62 g.) was refluxed with concentrated hydrochloric acid (6 c.c.) for 6 hours, yielding the required acid (0·12 g.), m. p. 185—186°, undepressed by a specimen prepared as below.

Methyl β-(*carbethoxymethylamino*)*propionate*. Ethyl aminoacetate (8·4 g.) was allowed to react with methyl β-chloropropionate (10 g.) for 3 days at room temperature, and then warmed on the water-bath for 2·5 hours. Sodium hydroxide solution (11·5 c.c.; 33%), water (14 c.c.), and ether (17·5 c.c.) were added, and the mixture was cooled to −10°. Anhydrous potassium carbonate was added until a thick paste was obtained; the ether was separated, dried and distilled, giving the required *ester* (5·0 g.), b. p. 153—154°/20 mm. (Found: C, 51·4; H, 8·1. $C_8H_{15}O_4N$ requires C, 50·8; H, 7·9%).

Hydrolysis. The ester (5 g.) was refluxed with concentrated hydrochloric acid (15 c.c.) for 1·5 hours, and the product was isolated through its lead salt (cf. Cocker and Lapworth, *loc. cit.*). The *amino-acid* was rubbed with alcohol, and crystallised from dilute alcohol as needles (1 g.), m. p. 184—186° (Found: C, 38·7; H, 6·9. $C_5H_9O_4N,\frac{1}{2}H_2O$ requires C, 38·5; H, 6·4%). Its p-*toluenesulphonyl* derivative gave m. p. 163°, undepressed when the sample was mixed with one prepared by the above alternative method (Found: C, 47·8; H, 5·1. $C_{12}H_{15}O_6NS$ requires C, 47·9; H, 5·0%).

3-*Cyano*-4-*pyrrolidone*. Powdered sodium (0·78 g.) was dissolved in a mixture of benzene (10 c.c.) and alcohol (2 c.c.). On cooling, the ester cyanide (III; R = H) (5·3 g.) was slowly added. The mixture was refluxed for 1 hour, cooled, and poured on ice. The calculated quantity (33·9 c.c.) of N-hydrochloric acid was added, and the aqueous layer was separated and evaporated to dryness in a vacuum-desiccator. The residue was extracted with alcohol and the solution passed through a column of alumina. The solution, on concentration, deposited 3-*cyano*-4-*pyrrolidone* (0·5 g.), m. p. 165—166° (Found: C, 54·7; H, 5·5. $C_5H_6ON_2$ requires C, 54·5; H, 5·4%).

The authors thank Imperial Chemical Industries Limited, Dyestuffs Division, for a gift of acrylonitrile.

TRINITY COLLEGE, DUBLIN. [*Received, October 27th*, 1951.]

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211. *Certain 2-Pyrrolidinoethyl Ketones.*

By S. W. PELLETIER and ALDEN D. JOSEY.

IN connection with the synthesis of a series of 3-aminopropyl benzoates for study as local anæsthetics, it became necessary to prepare some representative 2-pyrrolidinoethyl ketones as intermediates. Since the use of pyrrolidine in the Mannich reaction has been little studied, we investigated the reaction between pyrrolidine and several ketones known to give good yields of the corresponding piperidino-derivatives. Though the study has been interrupted, it seemed useful to record the satisfactory synthesis of two pyrrolidinoalkyl ketones by the Mannich reaction. β-Pyrrolidinopropiophenone hydrochloride was obtained in 40% yield from pyrrolidine hydrochloride, formaldehyde, and acetophenone; and 2-β-pyrrolidinopropionylthiophen hydrochloride was obtained in 74% yield from 2-acetylthiophen. Attempts to prepare solid pyrrolidino-derivatives of *cyclo*pentanone and 1- and 2-acetylnaphthalene by a similar procedure were unsuccessful.

Experimental.—M. p.s are corrected. Analyses are by E. Davis and K. Pih.

Pyrrolidine hydrochloride. Two brief references describe this compound as a very hydroscopic material which does not lend itself to analysis (Ladenburg, *Ber.*, 1887, **20**, 443; Petersen, *ibid.*, 1888, **21**, 291). Its preparation has not been described. When an ethereal solution of pyrrolidine was saturated with " anhydrous " hydrogen chloride, an oily slush resulted which gave little or no yield of product when used in the Mannich reaction. By working at low temperatures and using only the stoicheiometric amount of thoroughly dried hydrogen chloride, a crystalline product was obtained which gave good yields of product in the Mannich condensation. The following represents a superior method of preparation.

Hydrogen chloride, dried over sulphuric acid, was bubbled slowly into a solution of freshly distilled pyrrolidine (20·0 g., 0·28 mole; dried over potassium hydroxide) in absolute ether (200 ml.), cooled in solid carbon dioxide–acetone, until precipitation was just complete. The ether was decanted and the product (29·4 g., 98%) stored *in vacuo* over phosphoric oxide.

β-*Pyrrolidinopropiophenone hydrochloride*. A mixture of acetophenone (38·6 g., 0·30 mole), paraformaldehyde (10·0 g., 0·33 mole), and pyrrolidine hydrochloride (26·7 g., 0·25 mole) in absolute ethanol (50 ml.) was boiled under reflux for 3 hours, and then kept overnight in the refrigerator. 28·6 g. (41%) of a hygroscopic product were obtained, of m. p. 105°. Drying at 100° furnished material melting at 162—164°. Crystallization from ethanol–acetone (1 : 9) gave the *hydrochloride* as fine, white crystals melting at 163—164° (Found : C, 65·3; H, 7·6; N, 5·9. $C_{13}H_{17}ON,HCl$ requires C, 65·1; H, 7·6; N, 5·8%).

2-β-*Pyrrolidinopropionylthiophen hydrochloride*. Freshly distilled 2-acetylthiophen (20·0 g., 0·16 mole), paraformaldehyde (10·0 g.) and pyrrolidine hydrochloride (29·8 g.) in absolute ethanol were treated as described above, except that after one hour's heating paraformaldehyde (2·0 g.) was added to the reaction mixture. A similar addition was made after the third hour of heating. After being heated for a further 30 minutes, the mixture was kept in the refrigerator for 6 hours. The yield of *hydrochloride* melting at 95—110° was 28·8 g. (74%). Crystallization from ethanol–acetone (75% recovery) furnished white needles melting at 168·6—169·2° (Found : C, 54·3; H, 6·8; N, 5·9. $C_{11}H_{15}ON,HCl$ requires C, 53·75; H, 6·6; N, 5·7%).

NOYES CHEMICAL LABORATORY, UNIVERSITY OF ILLINOIS, URBANA, ILLINOIS.

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212. *Some New Amine Arylsulphonates.*

By L. BAUER, J. N. BAXTER, J. CYMERMAN, and W. J. SHELDON.

A NUMBER of new amine arylsulphonates and hydrochlorides, prepared in the course of other work, are described in the table below.

Reduction of 2-nitrodibenzofuran with zinc and calcium chloride, and of *p*-nitrodiphenylsulphone with stannous chloride and hydrochloric acid afforded, apart from the expected primary amines, the corresponding azoxy-compounds in 15% and 8% yield, respectively. Although formation of azoxy-compounds from nitro-compounds is generally regarded as occurring only in alkaline media, reduction of, *e.g.*, *o*-nitrobenzamide to the

Salt	M. p.	Solvent [1]	Formula	Found : N, %	Reqd. : N, %
p-*Aminoazobenzene toluene*-p-*sulphonate* [2]	187—189° *	P	$C_{19}H_{19}O_3N_3S$	11·4	11·3
p-Aminoazobenzene hydrochloride [3]	>360	E	$C_{12}H_{12}N_3Cl$	18·3	18·0
p-*Aminodiphenylammonium toluene*-p-*sulphonate*	207—208	P	$C_{19}H_{20}O_3N_2S$	7·6	7·85
p-*Aminodiphenylammonium chloride* [4] ...	240—241	M	$C_{12}H_{13}N_2Cl$	12·95	12·7
p-*Aminodiphenyl sulphide toluene*-p-*sulphonate*	183·5—184·5	P	$C_{19}H_{19}O_3NS_2$	3·65	3·75
p-*Aminodiphenyl sulphide hydrochloride*	197—198 *	M	$C_{12}H_{12}NSCl$	6·05	6·05
p-*Aminodiphenylsulphone toluene*-p-*sulphonate*	215	P	$C_{19}H_{19}O_5NS_2$	3·5	3·45
2-*Aminofluorene toluene*-p-*sulphonate* ...	271 *	P	$C_{20}H_{19}O_3NS$	4·45	4·0
p-*Phenoxyanilinium toluene*-p-*sulphonate*	180	W	$C_{19}H_{19}O_4NS$	4·1	3·9
p-cyclo*Hexylanilinium toluene*-p-*sulphonate*	273—274 *	W	$C_{19}H_{25}O_3NS$	4·3	4·0
2-*Aminodibenzofuran toluene*-p-*sulphonate*	255—256 *	W	$C_{19}H_{17}O_4NS$	3·9	3·9
p-*Aminodiphenylmethane toluene*-p-*sulphonate*	210—212	W	$C_{20}H_{21}O_3NS$	4·1	3·9
5-*Aminoacridinium toluene*-p-*sulphonate* [5]	261—262	M	$C_{20}H_{18}O_3N_2S$	7·8	7·6
2-*Aminothiazole benzenesulphonate*	135	A	$C_9H_{10}O_3N_2S_2$	10·4	10·85
2-*Aminopyrimidinium benzenesulphonate*	156	P	$C_{10}H_{11}O_3N_3S$	†	†
4 : 4′-*Diaminodiphenylsulphone dihydrochloride*	244—246 *	E	$C_{12}H_{14}O_2N_2SCl_2$	8·95	8·75

* M. p. with decomposition.

† Found : C, 47·6; H, 4·4; S, 12·7. Required : C, 47·4; H, 4·4; S, 12·65%.

[1] A = acetone; M = methanol; E = ethanol; P = *iso*propanol; W = water. [2] Red. [3] Violet. Morgan and Micklethwait (*J.*, 1907, **95**, 1513) do not record a m. p. [4] Blue-grey. [5] Yellow.

azoxy-compound in 10—15% yield by means of zinc dust and acetic acid is recorded by Heller (*Ber.*, 1910, **43**, 1913), and a number of aromatic nitro-compounds containing electron-attracting substituents are known to give azoxy-compounds with stannous chloride and hydrochloric acid (Flürscheim, *J. pr. Chem.*, 1905, **71**, 497), and zinc dust and sulphuric acid (Reissert and Grube, *Ber.*, 1909, **42**, 3711).

Experimental.—The arylsulphonates and hydrochlorides were prepared by standard methods; they crystallised in white needles unless otherwise indicated (table).

2 : 2′-*Azoxydibenzofuran.*—Reduction of 2-nitrodibenzofuran (30 g.) in aqueous alcohol (1000 c.c.; 80%) was effected by refluxing the solution with zinc (300 g.) and calcium chloride (10 g.) for 2 hours. The hot solution was filtered into water (2000 c.c.), and the yellow precipitate dried and extracted with acetone (150 c.c.) and ether (500 c.c.), giving 2-aminodibenzofuran in 65% yield. The residue (insoluble in acetone and ether) crystallised from benzene in orange needles, m. p. 271°, of 2 : 2′-*azoxydibenzofuran* (Found: C, 75·9; H, 3·8; N, 7·5. $C_{24}H_{14}O_3N_2$ requires C, 76·2; H, 3·7; N, 7·4%) in 15% yield.

pp′-*Diphenylsulphonylazoxybenzene.*—Reduction of *p*-nitrodiphenylsulphone (13·1 g.) in alcohol (130 c.c., 95%) by stannous chloride (37 g.) and hydrochloric acid (43 c.c., 10N) for 10 hours under reflux gave, on cooling, an orange solid (0·9 g., 8%) crystallising from methanol in orange needles, m. p. 262—263°, of the *azoxy*-compound (Found: C, 60·3; H, 3·9; N, 5·95. $C_{24}H_{18}O_5N_2S_2$ requires C, 60·25; H, 3·75; N, 5·85%).

This work was carried out under the auspices of the National Health and Medical Research Council, to whom we are indebted for financial assistance.

ORGANIC CHEMISTRY DEPARTMENT, UNIVERSITY OF SYDNEY. [*Received, November 19th*, 1951.]

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213. *A Correction to "Magnetochemistry of the Heaviest Elements. Part V. Uranium Tetrafluoride–Thorium Tetrafluoride Solid Solutions."*

By J. K. DAWSON.

OWING to arithmetical error the concentrations of the uranium in the solid solutions reported earlier (*J.*, 1951, 2889) were erroneous. Consequently, the susceptibilities and magnetic moments of the uranium ion derived from the gram-susceptibilities are considerably altered as shown in the following revised tables:

TABLE II.

Concentration, %	*T*, °K	$10^6\chi_g$.	$10^6\chi_m$.	$10^6\chi_{U(IV)}$	Composition, %	*T*, °K	$10^6\chi_g$.	$10\chi_m$.	$10^6\chi_{U(IV)}$
U, 100	90	22·39	7030	7091	U, 39·7	90	10·26	3186	8178
	197	14·61	4588	4649	Th, 60·3	199	5·94	1842	4791
	300	10·67	3530	3411		300	4·24	1317	3469
	332	9·92	3117	3176		328	3·76	1168	3094
U, 94·9	90	22·27	6988	7483	U, 20·6	90	5·66	1751	8807
Th, 5·1	200	13·41	4208	4555	Th, 79·4 ...	200	2·822	872·8	4535
	301	10·01	3141	3431		303	1·837	568·2	3054
	334	9·21	2889	3164		355	1·579	488·4	2667
U, 86·2	90	20·60	6453	7606	U, 10·4	90	2·903	896·3	9171
Th, 13·8 ...	199	12·60	3947	4701	Th, 89·6 ...	199	1·437	443·6	4831
	295	9·22	2888	3471		300	0·936	289·0	3347
	328	8·47	2653	3199		330·5	0·814	251·3	2986
U, 67·6	90	16·92	5301	7908					
Th, 32·4 ...	200	10·11	3165	4761					
	298	7·38	2303	3500					
	334	6·62	2066	3149					

TABLE III.

U, %	100	94·9	86·2	67·6	39·7	20·6	10·4
Δ	102	102	78	68	56	22	25
μ	3·30	3·30	3·20	3·17	3·11	2·82	2·92

Within experimental error, both the susceptibility at room temperature and the moment extrapolated to infinite dilution agree with the values predicted for two unpaired spins with the orbital contribution to the moment completely quenched ($\chi = 3333 \times 10^{-6}$, $\mu = 2{\cdot}83$). This result is very similar to that obtained in the urania–thoria solid solutions and is taken to imply an electron configuration of $6d^2$ for the uranous ion, since $5f$ electrons would be expected to exert some orbital contribution owing to the screening effect of the 6*s* and the $6p$ electrons.

ATOMIC ENERGY RESEARCH ESTABLISHMENT,
HARWELL, NEAR DIDCOT, BERKS.

[*Received, November 16th*, 1951.]

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214. *ω-Halogenomethyl-pyridines, -quinolines, and -isoquinolines. Part III.* The Reduction of ωωω-Tribromoquinaldine by Alcohol in the Presence of Sulphuric Acid.*

By A. ASTELL-BURT and D. LL. HAMMICK.

ωωω-TRIBROMOQUINALDINE can readily be reduced by conventional reagents (stannous bromide, etc.); it can also be converted smoothly into ωω-dibromoquinaldine and with rather more difficulty into ω-monobromoquinaldine by means of tetralin or other hydrocarbons, in processes which probably involve free radicals (Brown and Hammick, *J.*, 1950, 628: Brown, Grice, Hammick, and Thewlis, *J.*, 1951, 1149). Dirstine and Bergstrom (*J. Org. Chem.*, 1946, **11**, 55) reduced the tribromoquinaldine to the dibromo-compound by ethyl alcohol in the presence of excess of concentrated sulphuric acid; because of charring, they were unsuccessful with other alcohols. Sharp (*J. Pharm. Pharmacol.*, 1949, **1**, 395), apparently unaware of Dirstine and Bergstrom's work, has also effected 88% reduction to the dibromo-compound by ethyl alcohol and sulphuric acid.

In the strongly acid media used by the above workers homolytic reactions would appear to be unlikely and this view is confirmed by our experiments which show that in dilute alcoholic solutions of sulphuric acid the rate of reduction is proportional to the concentration of acid.

Experimental.—Our experience and that of other workers (see above) is that in both concentrated and dilute ethanolic solutions of sulphuric acid the reduction of ωωω-tribromoquinaldine is practically quantitative. It is not, however, possible to give more than a qualitative account of the oxidation products of the alcohol. The tribromo-compound boiled in alcohol in the absence of acid gives a small quantity of acetaldehyde (identified as its dinitrophenylhydrazone); in the presence of sulphuric acid a complex mixture of alcohol and brominated products is produced. These may result from the primary formation of acetaldehyde, which in fact reduces tribromoquinaldine very readily. About 20% of the bromine removed from the tribromo-compound can be recovered as ethyl bromide; bromoform can also be obtained by the action of alkali on the products of the oxidation of the alcohol. We have been less concerned with the fate of the bromine than with the effects of acidity on the rate of the reduction, and to this end we have followed the rate of reduction by ethyl alcohol at 100° alone and in the presence of increasing concentrations of sulphuric acid. Solutions (3 g. of tribromoquinaldine in 60 c.c. of ethyl alcohol) were sealed in glass tubes which were then heated for 1 hour in boiling water; the residual tribromoquinaldine was hydrolysed by refluxing the contents of the tubes with dilute aqueous sulphuric acid for several hours (dibromoquinaldine is untouched by such treatment). After partial neutralisation, quinaldinic acid was precipitated as the copper salt, which was washed, dried, and weighed. Control experiments showed that (i) hydrolysis of tribromoquinaldine to quinaldinic acid during the hour's heating at 100° was small (2%), and (ii) quinaldinic acid can be estimated to an accuracy of ±3% by the method adopted. The

* Part II, *J.*, 1951, 1149.

results are given in the following table, where the initial concentration of tribromoquinaldine is 0·132 mole/l.; and 60 c.c. of the solution were used in each experiment, equivalent to 0·153 mole

$[H^+]$, Mole/l.	0	0·025	0·050	0·20	0·250	0·50	1·00
X	1·334	1·315	1·290	1·200	1·148	1·036	0·832
$-\log_{10} X$	−0·1252	−0·1189	−0·1106	−0·0792	−0·0600	−0·0149	+0·0799

copper quinaldinate; X is the quantity in g. of copper quinaldinate obtained from tribromoquinaldine remaining after 1 hour. $T = 100°$.

It will be seen that even in the absence of acid, reduction is considerable. By denoting the concentration of tribromoquinaldine as [A], we can tentatively write, for a solution containing an excess of alcohol:

$$-d[A]/dt = k_1[A] + k_2[A][H^+]$$

Bearing in mind that any quantity of tribromoquinaldine is proportional to the weight, X, of copper quinaldinate into which it can be converted, we have, for unit time $dt = 1$ hour, $-\log_{10} X = a + b[H^+]$. A satisfactory straight line can be drawn through the plot of $-\log X$ against $[H^+]$.

A few experiments have been carried out with other alcohols. As might be expected, *iso*-propyl alcohol reduces tribromoquinaldine much more rapidly than does ethyl alcohol; under the same conditions, methyl and *tert.*-butyl alcohols are practically unreactive.

DYSON PERRINS LABORATORY, UNIVERSITY OF OXFORD. [*Received, November 30th*, 1951.]

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215. *The Degradation of the Side Chain of Lanostadienol.*

By R. G. CURTIS and H. SILBERMAN.

A DESCRIPTION of work done in this laboratory on the degradation of the side chain of lanostadienol is made desirable by the appearance of a paper by Voser, Mijovic, Jeger, and Ruzicka (*Helv. Chim. Acta*, 1951, **34**, 1585) on this subject. As these authors have emphasized, one of the difficulties of this side-chain degradation has been the small yield of trisnorlanostenolic acid obtained when lanostadienol is ozonised. However, by modification of the conditions of ozonolysis it has now been found that a 30% yield of the acid can be obtained from the mixed wool-wax triterpenes; that is a 60% conversion of the lanostadienol content. It thus seemed possible to degrade the side chain without oxidation of the four-ring system in the neighbourhood of the "inactive" double bond; the method of approach thus differed from that described by Voser *et al.* One cycle of a Wieland degradation has been completed, giving the acid, $C_{26}H_{42}O_3$, lacking four of the side-chain carbon atoms of lanostadienol.

Attempts were also made to degrade the chain by bromination, and the monobromolanostadienol (I) was obtained in good yield. The bromine atom is extremely inert; that it

$$(C_{25}H_{41}O)—CH_2·CBr{:}CMe_2 \quad (I)$$

is located as formulated, follows from the conversion of (I) by ozonolysis into trisnorlanostenolic acid and from the ready reduction of (I) to lanostenol.

Experimental.—Trisnorlanostenolic acid. Wool-wax triterpenes (10 g.) in chloroform (200 ml.) were ozonised (10 minutes; 6 l. of oxygen containing 5% of ozone) at 0°. Water (100 ml.) was added to the solution, and the chloroform then removed by distillation. The ozonide was decomposed by refluxing it for 12 hours with 1·0*N*-ethanolic sodium hydroxide (200 ml.) and hydrogen peroxide (10 ml.), the solvents were distilled under reduced pressure, and the last traces of water were removed azeotropically with benzene. The residual, dried sodium salt was washed with ether in an extractor and dissolved in aqueous ethanol, and the solution acidified with mineral acid. The crude acid was washed with a little chloroform–methanol (1 : 1) and crystallised from ethyl acetate, forming fine needles (3·2 g.), m. p. 260—261°.

Methyl trisnorlanostenolate. A solution of diazomethane in ether at 0° was added to one of the acid (5 g.) in acetone (120 ml.) and chloroform (120 ml.). After the excess of diazomethane

had been distilled into acetic acid, the solvents were removed until the methyl ester began to crystallise; it (4·6 g.) formed needles, m. p. 155°, $[\alpha]_D^{21}$ +58·4° (*c*, 3·0 in chloroform).

27 : 27-*Diphenyltrisnorlanosten*-2 : 27-*diol*.* Phenylmagnesium bromide, prepared from magnesium (4 g.), bromobenzene (17 ml.), and ether (250 ml.), was added slowly to methyl trisnorlanostenolate (4·6 g.) dissolved in anisole (250 ml.); the ether was then distilled off and the anisole solution heated at 100° for 5 hours. After the mixture had cooled to 0° and had been decomposed with ice-cold dilute sulphuric acid, the anisole layer was separated and washed with water until neutral. The anisole and diphenyl were removed by steam-distillation and the residue was filtered off and refluxed in 1·0N-ethanolic sodium hydroxide solution (400 ml.) for 4 hours. Water (400 ml.) was added and the neutral material was extracted into benzene and crystallised from methanol. The *diol* formed needles (3·7 g.), m. p. 172°, which solidified again at 174° and finally re-melted at 197—198°, $[\alpha]_D^{20}$ +52·3° (*c*, 1·5 in chloroform) (Found: C, 84·7; H, 9·5. $C_{39}H_{54}O_2$ requires C, 84·9; H, 9·5%).

27-*Hydroxy*-27 : 27-*diphenyltrisnorlanosten*-2-*yl acetate*. The 2 : 27-diol (3·7 g.), pyridine (20 ml.), and acetic anhydride (20 ml.) were heated for 2 hours on a steam-bath and finally refluxed (30 minutes). The solution was poured into cold water, and the precipitated *acetate* crystallised from acetic acid. It formed needles (3·8 g.), m. p. 220—221°, $[\alpha]_D^{20}$ +59·3° (*c*, 3·0 in chloroform) (Found: C, 82·6; H, 9·0. $C_{41}H_{56}O_3$ requires C, 82·5; H, 9·0%).

Dehydration of 27-*hydroxy*-27 : 27-*diphenyltrisnorlanosten*-2-*yl acetate*. The alcohol (5 g.), glacial acetic acid (300 ml.), and acetic anhydride (20 ml.) were refluxed for 24 hours; on cooling 27 : 27-*diphenyltrisnorlanosta*-9 : 26-*dien*-2-*yl acetate* separated. It formed glistening plates (4·8 g.), m. p. 207—208°, $[\alpha]_D^{20}$ +65° (*c*, 1·5 in chloroform) (Found: C, 84·9; H, 9·1. $C_{41}H_{54}O_2$ requires C, 85·1; H, 9·4%).

The C_{26} *acid*. The diphenylethylene compound (2 g.), m. p. 207—208°, was ozonised as described for the preparation of trisnorlanostenolic acid. The *tetrakisnorlanostenolic acid* crystallised from chloroform–methanol (2 : 1) in needles (0·2 g.); these contained methanol of crystallisation which was evolved on melting; m. p. 258—259°, $[\alpha]_D^{20}$ +36° (*c*, 1·0 in chloroform) (Found, on a sample dried in a vacuum at 140° for 8 hours: C, 77·6; H, 10·2. $C_{26}H_{42}O_3$ requires C, 77·6; H, 10·5%). The *methyl* ester had m. p. 156—157° (Found: C, 77·5; H, 10·5. $C_{27}H_{44}O_3$ requires C, 77·8; H, 10·7%).

27-*Bromolanostadienol*. A solution of bromine (2·3 ml.) in glacial acetic acid (140 ml.) was added at 0° to wool-wax triterpenes (25 g.) in ether (500 ml.). After 24 hours the excess of bromine was destroyed by the addition of sodium hydrogen sulphite solution, and the ether removed. The crystalline material was filtered off, washed with water and then with methanol, and refluxed for 4 hours in 1·0N-ethanolic alkali (700 ml.). On cooling, fine needles (18 g.), m. p. 172—175°, separated. These were washed with methanol and recrystallised first from ethanol, then from *iso*propanol, and finally several times from chloroform–methanol (1 : 1), giving the pure 27-*bromolanostadienol* (9 g.), m. p. 196—198°, $[\alpha]_D^{20}$ +51·4° (*c*, 3·0 in chloroform) (Found: C, 70·8; H, 9·6. $C_{30}H_{49}OBr$ requires C, 71·2; H, 9·8%).

Ozonolysis of 27-bromolanostadienol (1 g.) by the method used for the preparation of trisnorlanostenolic acid from wool-wax triterpenes yielded this acid (0·5 g.), m. p. 260—261°, and bromine.

Reduction of 27-bromolanostadienol (0·5 g.) in ethanol (100 ml.) at 100° with Raney nickel catalyst yielded lanostenol, which crystallised from methanol (15 ml.) and benzene (3 ml.). It formed needles (0·3 g.), m. p. 146—147°, $[\alpha]_D^{20}$ +58° (*c*, 3·0 in chloroform).

This work was carried out as part of the research programme of this Division.

Division of Industrial Chemistry,
C.S.I.R.O., Box 4431, G.P.O., Melbourne.

[*Received, December 11th*, 1951.]

* The side chain is here numbered outwards from its point of attachment to the nucleus, so that the terminal carbon atoms are numbered 29 and 30. This avoids assumption of the position at which it is attached to the nucleus and also of more of the nature of the side chain than has been rigidly proved.

216. *A Linear Acetal of Ethylene Glycol.*

By J. D. Bryan.

Certain batches of commercial ethylene glycol were thought to contain traces of 1 : 1-bis-2′-hydroxyethoxyethane (II), the linear acetal of the glycol. The note describes the synthesis of this compound, no mention of which could be found in the literature.

The corresponding acetate (I) was obtained in 18% yield by the reaction of acetylene with ethylene glycol monoacetate under anhydrous conditions in the presence of mercuric

(I) $CH_3{\cdot}CH(O{\cdot}CH_2{\cdot}CH_2{\cdot}O{\cdot}CO{\cdot}CH_3)_2$ $CH_3{\cdot}CH(O{\cdot}CH_2{\cdot}CH_2{\cdot}OH)_2$ (II)

oxide and methanolic boron trifluoride (Neiuwland, Vogt, and Foohey, *J. Amer. Chem. Soc.*, 1930, **52**, 1018; Coffman, U.S.P. 2 387 495). Treatment of this compound with excess of methanol containing sodium methoxide as a catalyst gave the required acetal (II).

Experimental.—The microanalysis is by Drs. Weiler and Strauss, Oxford.

1 : 1-*Bis*-2′-*acetoxyethoxyethane* (I). Red mercuric oxide (1 g.) was partly dissolved in a 55—65% solution of boron trifluoride in methanol (5 g.) by gentle heat. Ethylene glycol monoacetate (160 g.) was then added and dry acetylene passed over the stirred mixture at 25—30° until the calculated quantity (20 g.) had been absorbed. The mixture was cooled to 10° and stirred for 10 minutes with anhydrous sodium carbonate (10 g.). Saturated aqueous sodium carbonate (25 ml.) was then added and the mixture extracted with ether. The residue, obtained on removal of the ether from the dried (K_2CO_3) extract, was fractionated under reduced pressure; the second fraction, b. p. 108°/0·8 mm., immiscible with water, was 1 : 1-bis-2′-acetoxyethoxyethane. The saponification value of the product indicated a purity of 98·6%.

1 : 1-*Bis*-2′-*hydroxyethoxyethane* (II). The acetate (I) (30 g.) was refluxed with absolute methanol (100 ml.) and 0·1N-sodium methoxide solution (12 ml.) for 6 hours. The residue obtained on removal of methyl acetate and methanol was distilled under reduced pressure to give 1 : 1-*bis*-2′-*hydroxyethoxyethane* (15 g.), b. p. 100°/0·5 mm., n_D^{25} 1·4467, d_4^{25} 1·1088 (Found : C, 48·3; H, 9·3. $C_6H_{14}O_4$ requires C, 48·0; H, 9·4%). The product was hygroscopic.

Hydrolysis of 1 : 1-*bis*-2′-*hydroxyethoxyethane*. The acetal (4 g.) was shaken with cold 1·0N-sulphuric acid (50 ml.) in a stoppered flask for 15 minutes. After neutralisation with sodium hydroxide solution, treatment of the solution with dimedone gave the derivative of acetaldehyde, m. p. 141°; benzoylation gave ethylene glycol dibenzoate, m. p. 73°.

British Cellophane, Ltd., Bridgwater, Somerset. [*Received, November 10th*, 1951.]

OBITUARY NOTICES.

H. E. COX.

1892—1951.

Dr. H. E. Cox died in hospital on November 21st, 1951, as the result of a street accident.

Henry Edward Cox was born at Lowestoft in 1892. He was educated at St. Paul's School, but left at the age of 16 to spend the next two years with John Bell and Croyden. He then became an assistant in the famous Allen laboratory in Sheffield. It was in 1879 that Alfred Henry Allen published the first volume of the first edition of " Commercial Organic Analysis," an attempt to bring together all that was then known about general commercial organic analysis, this being pioneer work except for a small volume of less than 200 pages entitled " Outlines of Proximate Organic Analysis," by Prof. Prescott, of Michigan, in 1875. The completion of this edition and its revision occupied Allen until the time of his death in 1904. The revision still continues with the aid of many specialists, and edition has followed edition. This activity, steadily pursued in this great laboratory, must have had a very great influence in determining the direction of Cox's life work during the seven years of early manhood that he spent there; whenever he referred to Sheffield in conversation he did so always in terms of affection and respect. While there he qualified as an Associate of the Institute of Chemistry. In 1917 he joined Rudd Thompson in Newport, and during the next ten years he gained the London University degree of Ph.D., became a Fellow of the Institute of Chemistry, and was appointed Deputy Public Analyst to Rudd Thompson for the County of Monmouth. He also acted as an abstractor to *The Analyst*, and it is likely that it was through the agency of Ainsworth Mitchell, Editor of *The Analyst* from 1920 onwards and in close touch with Otto Hehner, that in 1923 he joined the latter in partnership as Hehner and Cox; this analytical and consulting practice was established at 11, Billiter Square, London. Hehner had left England in 1921 for change and rest in South Africa, where his son was engaged in farming, but the death of his then partner R. G. Grimwood in 1922 brought him back; he resumed active work with Cox, only to return, however, almost immediately to South Africa where he died in 1924. Cox was then left as the only principal in the practice, and he remained so until the time of his death. He was appointed Public Analyst for Hampstead in 1925 and later for Cornwall and the Isles of Scilly. In 1934 he was awarded the D.Sc. of London University. The second world war inflicted a very hard blow; his laboratory was destroyed during an air-raid in 1941. Cox was too strong in character, and too resilient in reaction, to permit this disaster to deter him from his life's work but it required a great resolution because the destruction was complete. I remember very well one day, when we were standing side by side in Billiter Square, watching the men digging into the heap of rubble and ashes, how depressed we became as one of the men came up with a rescued object: a platinum basin battered and shapeless and black with soot; for this, of a verity, meant certain loss of all his records and books. The only bright spot was that he was able immediately to reconstruct his laboratory next door at No. 10 and here he continued his practice until his death.

Cox possessed very great energy, both mental and physical, much of which was devoted to loyal service to the many scientific Societies to which he belonged. He was elected to the Chemical Society in 1916 and became Chairman of the Joint Library Committee in 1948, a position which he held to the time of his death. By virtue of this appointment he was an ex-officio Member of Council. He was also a Member of Council of the Society of Chemical Industry, having held the high office of Vice-President, and was active on many of the Committees. Perhaps he found his greatest pleasure in this Society in the work of its very active and greatly esteemed Food Group, and he and Mrs. Cox were unfailing attendants at all the social occasions. Indeed no summer tour by the Food Group would have been deemed complete without Dr. and Mrs. Cox and the faithful camera, and no reunion without photographs from the latter. To the Society of Public Analysts he gave similar service, as Vice-President and on Council and Committees; and he was the first choice of the Society whenever any Government or Ministerial Enquiry or Committee called for representatives. His last activities in this connexion were as a Member of the Government enquiry now concerned with the Preservative Regulations, and as a Member of the Joint Negotiating Committee of Local Authorities and Public Analysts. The Royal Institute of Chemistry owed much to him for service on Council and for the maximum period as an Examiner for the Fellowship in Branch E.

Cox often held very firm opinions on policy, procedure, or domestic economy in these various Societies but he was never harsh or dogmatic. His somewhat disarming smile was a characteristic accompaniment of the exposition of his views. It happened occasionally that these were against the general views or feelings, but however much in the minority he would regard it as a duty to give his opinion. He rarely seemed to lose his temper. He was highly esteemed and in considerable demand as an expert witness on scientific matters and doubtless this capability of controlling his temper was a great asset under severe cross-examination.

His literary output was very considerable. He had contributed to the " Encyclopaedia Britannica," and had revised, and almost completely re-written, Wynter Blyth's " Foods—Composition and Analysis." His personal work, " The Chemical Analysis of Foods," has run into three editions, and has been accepted on many occasions in Courts of Law as an authority for definitions, standards of composition, and methods of analysis in proceedings under the Food and Drugs Act. He also wrote a large number of articles for the various scientific journals.

In his private practice as an analytical chemist and consultant, Cox specialised in several fields, particularly the chemical investigations arising under patent litigation, and the examination of dyed materials in connexion with cases of dermatitis. The destruction of his laboratory in 1941 caused a temporary halt in his patent work as the whole of his records dealing with patent-law cases were destroyed—an irreplaceable loss—but he soon made progress again.

Edward Cox was a devout churchman and served the office of head churchwarden. In the tribute paid by his Vicar, when a full church at the funeral bore testimony to the respect and affection in which he was held, it was recalled with deep emotion that on the Sunday before his death he had served his office to them by reading the morning lessons.

He was a member of the Savage and the Chemical Club, having assisted greatly in the formation and early growth of the latter. At home he was the centre of an active social life, a kindly atmosphere always extended with the utmost cordiality to professional brethren visiting London. Locally he was in demand to explain scientific matters to district meetings in non-scientific terms and he undoubtedly had a flair in this direction.

He married in 1922, and is survived by Mrs. Cox, one son, and two daughters.

GEORGE TAYLOR.

CHARLES KENNETH TINKLER.

1881—1951.

By the death on October 25th, 1951, of Dr. C. K. Tinkler, formerly Professor of Chemistry at King's College of Household and Social Science, University of London, the Chemical Society has lost a Fellow of 44 years' standing and a former member of Council (1930—1933). He will long be missed in many circles, particularly in the world of women's education—a world in which he ranked as a pioneer.

He was born at Shrewsbury in 1881 and received his early education at Caterham School. After graduating from the University College of North Wales, Bangor, he went to the University of Edinburgh to work under Professor J. J. Dobbie with whom he published a number of papers in the *Journal* on cotarnine and related compounds and on the relation between ultra-violet absorption spectra of certain diazo-compounds and their chemical constitution.

He became a lecturer in the University of Birmingham in 1904 in Professor P. F. Frankland's department, and during the following eleven years worked intensively both in teaching and research; he published a series of papers in the *Journal* on topics related to alkaloids of the berberine type and cognate compounds. Towards the end of this period he became interested in the composition and utilisation of fuels, and in collaboration with a fellow Lecturer published a book much valued in the petroleum industry: " Chemistry of Petroleum," by Tinkler and Challenger.

In 1915 he was appointed a Reader in the University of London and Head of the Chemistry Department of King's College of Household and Social Science, then the Home Science Department of King's College for Women. It was to the work and development of this College that he devoted the thirty-two years of his professional career remaining until his retirement in 1947.

To understand fully the main achievements of Professor Tinkler's life it is necessary to look at the history of the College with which he was so closely identified. At the time of his appoint-

ment the College was in its infancy. Only seven years previously, in 1908, a course dealing with the scientific and social aspects of the household and institution had been run for the first time in a department of King's College for Women, a branch of King's College, Strand. The new, and at that time, revolutionary curriculum was devised and initiated by a few men of vision, Sir John Atkins, Sir Cooper Perry, Sir Hubert Jackson, and Professor Smithells, who were convinced of the scope and necessity for this type of education for women.

It was by a stroke of good fortune that Dr. Tinkler became a member of the small staff in 1915, for he too possessed the same ideas and foresaw the expansion which has since taken place in every branch of the field covered by the curriculum : for example, in the science of foods, detergents, and fuels, and even in the study of the social and economic relation of the home to the community and the nation.

His arrival took place at the opportune moment when the first instalment of the new building on Campden Hill, Kensington, had been erected but the laboratories were not yet equipped. The situation was calling for those qualities with which Professor Tinkler was well endowed—organising ability, initiative, and enthusiasm born of his ever-increasing and infectious faith in the whole project. He became a leading spirit in developing the course and establishing the College and its work. His personality combined with wisdom and knowledge rendered him an invaluable committee member, an able representative of the College in the outside world, and the man to whom people instinctively turned for guidance in all matters whether academic, practical, or administrative.

Success came with the years : in 1920 a professorship was conferred upon him by the University, in 1921 the course was recognised by the University by the granting of the degree B.Sc. (Household and Social Science), and in 1928 the College was recognised as an independent school of the University and given its present title.

Within his own department he applied himself from 1915 onwards to the task of devising a suitable course in Chemistry to dovetail with the other subjects in the curriculum. In collaboration with Miss Helen Masters he created a course in Applied Chemistry unique in its scope and to the present day regarded as a model in Home Science departments throughout the world. The results of original work were embodied in this course from time to time. The practical work and some of the better established aspects of theory were published in two volumes : " Applied Chemistry," by Tinkler and Masters.

As a teacher, Professor Tinkler excelled. He possessed a great store of knowledge of a wide range of practical matters, a remarkable gift of clear exposition, and a rare capacity for bridging the gap between the academic and practical aspects of his subject.

He is survived by a widow and one son.

A. Jackman.

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